TITLE OF THE INVENTION

(METHYLSULFONYL)PHENYL-2-(5H)-FURANONES AS COX-2 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application serial no. 08/728,512 filed on October 9, 1996, abandoned, which was based upon provisional application nos. 60/005,371 filed on October 13, 1995 and 60/011,637 filed on February 14, 1996, priority of which is claimed hereunder.

BACKGROUND OF THE INVENTION

This invention relates to methods of treating cyclooxygenase mediated diseases and certain pharmaceutical compositions therefor.

Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Initially, only one form of cyclooxygenase was known, this corresponding to cyclooxygenase-1 (COX-1) or the constitutive enzyme, as originally identified in bovine seminal vesicles. More recently the gene for a second inducible form of cyclooxygenase, cyclooxygenase-2 (COX-2) has been cloned, sequenced and characterized initially from chicken, murine and human sources. This enzyme is distinct from the COX-1 which has been cloned, sequenced and characterized from various sources including the sheep, the mouse and man. The second form of cyclooxygenase, COX-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both physiological and pathological roles, we have concluded that the constitutive enzyme, COX-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, COX-2, is mainly

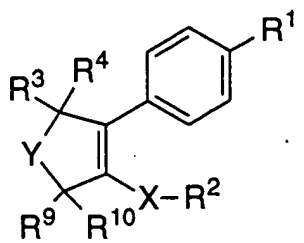
responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of COX-2 will have similar antiinflammatory, antipyretic and analgesic properties to a conventional non-steroidal antiinflammatory drug, and in addition would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

Furthermore, such a compound will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labour, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, for decreasing bone loss particularly in postmenopausal women (i.e. treatment of osteoporosis) and for the treatment of glaucoma.

A brief description of the potential utility of cyclooxygenase-2 inhibitors is given in an article by John Vane, Nature, Vol. 367, pp. 215-216, 1994, and in an article in Drug News and Perspectives, Vol. 7, pp. 501-512, 1994.

SUMMARY OF THE INVENTION

The invention encompasses the novel compound of Formula I as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.



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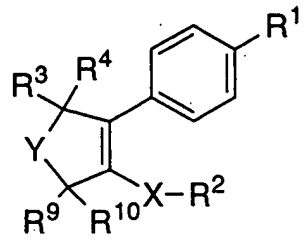
The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses the novel compound of Formula I as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.



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or a pharmaceutically acceptable salt thereof

wherein:

X is selected from the group consisting of

(a) CH_2,

(b) CHOH,

(c) CO,

(d) O,

(e) S, and

(f) $N(R^{15})$,

with the proviso that when R^3 and R^4 are other than

(1) both hydrogen,

(2) both C_{1-10} alkyl, or

(3) joined together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, then

X is selected from CO, O, S or $N(R^{15})$;

Y is selected from the group consisting of

(a) $C(R^{11})(R^{12})$,
(b) CO,
(c) O, and
(d) S;

R^1 is selected from the group consisting of
(a) SO_2CH_3,
(b) $SO_2NR^{16}R^{17}$,
(c) $SO_2NHC(O)CF_3$,
(d) $S(O)(NH)NH_2$,
(e) $S(O)(NH)NHC(O)CF_3$,
(f) $P(O)(CH_3)NH_2$, and
(g) $P(O)(CH_3)_2$,

R^2 is selected from the group consisting of
(a) C_{1-10}alkyl,
(b) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of
(1) hydrogen,
(2) halo,
(3) C_{1-10}alkoxy,
(4) C_{1-10}alkylthio,
(5) CN,
(6) C_{1-6} fluoroalkyl
(7) C_{1-10} alkyl,
(8) N_3,
(9) $-CO_2H$,
(10) $-CO_2-C_{1-10}$alkyl,
(11) $-C(R^5)(R^6)-OH$,
(12) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and
(13) $-C_{1-6}$alkyl$-CO_2-R^5$,
(14) benzyloxy,
(15) $-O-(C_{1-6}$alkyl$)-CO_2R^5$, and
(16) $-O-(C_{1-6}$alkyl$)-NR^5R^6$,
(c) mono- , di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said

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ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or
the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, or 3 additional N atoms, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-10}alkyl,
(4) C_{1-10}alkoxy,
(5) C_{1-10}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) $-C(R^5)(R^6)-OH$,
(10) $-C(R^5)(R^6)-O-C_{1-10}$alkyl, and
(11) C_{1-6}fluoroalkyl;

(d) a mono- or di- substituted benzoheterocycle in which the heterocycle is a 5, 6, or 7-membered ring which may contain 1 or 2 heteroatoms chosen independently from O, S, or N and which may contain a carbonyl group or a sulfonyl group; wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-10}alkyl,
(4) C_{1-10}alkoxy,
(5) C_{1-10}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) $-C(R^5)(R^6)-OH$,
(10) $-C(R^5)(R^6)-O-C_{1-10}$alkyl, and
(11) C_{1-6}fluoroalkyl;

(e) a heterocycloalkyl group of 5, 6 or 7 members which contains 1 or 2 heteroatoms chosen from O, S, or N and optionally contains a carbonyl group or a sulfonyl group.

(f) a mono- or di- substituted benzocarbocycle in which the carbocycle is a 5, 6, or 7-membered ring which optionally contains a carbonyl group, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-10}alkyl,
(4) C_{1-10}alkoxy,
(5) C_{1-10}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) $-C(R^5)(R^6)-OH$,
(10) $-C(R^5)(R^6)-O-C_{1-10}$alkyl, and
(11) C_{1-6}fluoroalkyl;

(g) a mono- or di-substituted bicyclic heteroaryl of 8, 9, or 10 members, containing 2 to 5 heteroatoms chosen independently from O, S or N, and in which each ring contains at least one heteroatom, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-10}alkyl,
(4) C_{1-10}alkoxy,
(5) C_{1-10}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) $-C(R^5)(R^6)-OH$,
(10) $-C(R^5)(R^6)-O-C_{1-10}$alkyl, and
(11) C_{1-6}fluoroalkyl;

R^3 is hydrogen, C_{1-10} alkyl, CH_2OR^7, CN, CH_2CN, C_{1-6}fluoroalkyl, F, $CON(R^7)_2$, mono- or di-substituted phenyl, mono or di-substituted benzyl, mono- or di-substituted heteroaryl, mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkyl,
(4) C_{1-6}alkoxy,
(5) C_{1-6}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) $-C(R^5)(R^6)-OH$,
(10) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and
(11) C_{1-6}fluoroalkyl;

R^4 is

(a) hydrogen
(b) C_{1-10}alkyl,
(c) C_{1-10}alkoxy,
(d) C_{1-10}alkylthio,
(e) -OH,
(f) $-OCOR^7$,
(g) -SH,
(h) $-SCOR^7$,
(i) $-OCO_2R^8$,
(j) $-SCO_2R^8$,
(k) $OCON(R^7)_2$,
(l) $SCON(R^7)_2$, and
(m) C_{1-6}fluoroalkyl;

or R^3 andR^4 together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^5 and R^6 are each independently selected from the group consisting of

(a) hydrogen, and

(b) C_{1-10}alkyl,

or R^5 and R^6 together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6 or 7 atoms;

each R^7 is independently selected from the group consisting of

(a) hydrogen,

(b) C_{1-6}alkyl,

(c) phenyl or monosubstituted phenyl wherein the substituents may be halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, CN, or CF_3, and

(d) benzyl or monosubstituted benzyl wherein the substituents may be halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, CN, or CF_3, or

two R_7 groups taken together with the nitrogen to which they are attached form a saturated monocyclic ring of 5, 6 or 7 atoms, optionally containing an additional O, S or NR^5;

each R^8 is independently selected from the group consisting of

(a) C_{1-6}alkyl,

(b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, CN, or CF_3, and

(c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, CN, or CF_3;

R^9 and R^{10} are independently selected from the group consisting of:

(a) hydrogen, and

(b) C_{1-7}alkyl, or

R^9 and R^{10} together with the carbon atom to which they are attached form a carbonyl or thiocarbonyl group;

R^{11} and R^{12} are independently

(a) hydrogen,

(b) mono- or di-substituted phenyl or mono- or di-substituted benzyl or mono- or di-substituted heteroaryl or mono- or di-

substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) fluoro, chloro, bromo and iodo,
(3) C_{1-6}alkyl,
(4) C_{1-6}alkoxy,
(5) C_{1-6}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) $-C(R^{13})(R^{14})-OH$,
(10) $-C(R^{13})(R^{14})-O-C_{1-4}$alkyl, and
(11) C_{1-6}fluoroalkyl, or

(c) C_{1-7}alkyl, CH_2OR^7, CN, CH_2CN, C_{1-6}fluoroalkyl, $CON(R^7)_2$, F, or OR^7; or

R^{11} and R^{12} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^{13} and R^{14} are independently selected from the group consisting of:

(a) hydrogen,
(b) C_{1-7}alkyl, or

R^{13} and R^{14} together with the carbon to which they are attached form a carbonyl, -C(=S)-, or a saturated monocyclic carbon ring of 3, 4, 5, 6, or 7 atoms.

R^{15} is selected from the group consisting of:

(a) hydrogen,
(b) C_{1-10}alkyl,
(c) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-10}alkoxy,
(4) C_{1-10}alkylthio,
(5) CN,

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(6) C_{1-6} fluoroalkyl
(7) C_{1-10} alkyl,
(8) N_3,
(9) $-CO_2H$,
(10) $-CO_2-C_{1-10}$alkyl,
(11) $-C(R^5)(R^6)-OH$,
(12) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and
(13) $-C_{1-6}$alkyl$-CO_2-R^5$;
(14) benzyloxy,
(15) $-O-(C_{1-6}$alkyl$)-CO_2R^5$, and
(16) $-O-(C_{1-6}$alkyl$)-NR^5R^6$,

(d) mono- , di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or
the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, or 3 additional N atoms, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-10}alkyl,
(4) C_{1-10}alkoxy,
(5) C_{1-10}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) $-C(R^5)(R^6)-OH$,
(10) $-C(R^5)(R^6)-O-C_{1-10}$alkyl, and
(11) C_{1-6}fluoroalkyl;

(e) a mono- or di- substituted benzoheterocycle in which the heterocycle is a 5, 6, or 7-membered ring which may contain 1 or 2 heteroatoms chosen independently from O, S, or N and which may contain a carbonyl group or a sulfonyl group;

wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-10}alkyl,
(4) C_{1-10}alkoxy,
(5) C_{1-10}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) $-C(R^5)(R^6)-OH$,
(10) $-C(R^5)(R^6)-O-C_{1-10}$alkyl, and
(11) C_{1-6}fluoroalkyl;

(f) a heterocycloalkyl group of 5, 6 or 7 members which contains 1 or 2 heteroatoms chosen from O, S, or N and optionally contains a carbonyl group or a sulfonyl group.

(g) a mono- or di- substituted benzocarbocycle in which the carbocycle is a 5, 6, or 7-membered ring which optionally contains a carbonyl group, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-10}alkyl,
(4) C_{1-10}alkoxy,
(5) C_{1-10}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) $-C(R^5)(R^6)-OH$,
(10) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and
(11) C_{1-6}fluoroalkyl;

R^{16} and R^{17} are independently selected from the group consisting of

(a) hydrogen
(b) C_{1-10}alkyl,

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(c) C_{1-10}alkanoic acid,
(d) C_{1-10}alkyl amine,
(e) phenyl or monosubstituted phenyl wherein the substituents are halo, C_{1-10}alkyl, C_{1-10}alkoxy, C_{1-10}alkylthio, C_{1-10}alkanoic acid, C_{1-10}alkylamine, CN, CO_2H or CF_3, and
(f) benzyl or monosubstituted benzyl wherein the substituents are halo, C_{1-10}alkyl, C_{1-10}alkoxy, C_{1-10}alkylthio, C_{1-10}alkanoic acid, C_{1-10}alkylamine, CN, CO_OH or CF_3, or

R16 and R17 together with the nitrogen to which they are attached form a saturated monocyclic ring of 5, 6 or 7 atoms, optionally containing an additional O, S or NR^5.

Within this embodiment there is a genus of compounds wherein

R^9 and R^{10} together with carbon atom to which they are attached form a carbonyl.

Within this genus there is a class of compounds wherein

X is O;
Y is O;
R^1 is selected from the group consisting of
(a) SO_2CH_3,
(b) $S(O)_2NR^{16}R^{17}$, and
(c) $S(O)(NH)NH_2$;
R^2 is selected from the group consisting of
mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of
(1) hydrogen,
(2) halo,
(3) C_{1-4}alkoxy,
(4) C_{1-4}alkylthio,
(5) CN,
(6) C_{1-3} fluoroalkyl
(7) C_{1-4} alkyl,

(8) $-CO_2H$,
(9) $-CO_2-C_{1-10}$alkyl,
(10) $-C(R^5)(R^6)-OH$,

R^3 is hydrogen, C_{1-6} alkyl, CH_2OR^7, CN, CH_2CN, C_{1-4}fluoroalkyl, F, $CON(R^7)_2$, mono- or di-substituted phenyl, mono or di-substituted benzyl, mono- or di-substituted heteroaryl, mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-4}alkyl,
(4) C_{1-4}alkoxy,
(5) C_{1-4}alkylthio,
(6) CN,
(7) CF_3,
(8) $-C(R^5)(R^6)-OH$, and

R^4 is

(a) hydrogen
(b) C_{1-6}alkyl,
(c) C_{1-6}alkoxy,
(d) C_{1-6}alkylthio,
(e) -OH,
(f) $-OCOR^7$,
(g) $-SCOR^7$,
(h) $-OCO_2R^8$, and
(i) $-SCO_2R^8$,

or R^3 andR^4 together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^5 and R^6 are each independently selected from the group consisting of

(a) hydrogen, and
(b) C_{1-6}alkyl,

or R^5 and R^6 together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6 or 7 atoms;

each R^7 is independently selected from the group consisting of

(a) hydrogen,

(b) C_{1-4}alkyl,

(c) phenyl or monosubstituted phenyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3, and

(d) benzyl or monosubstituted benzyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3

each R^8 is independently selected from the group consisting of

(a) C_{1-4}alkyl,

(b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3, and

(c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3;

R^9 and R^{10} together with the carbon to which they are connected form a carbonyl;

R^{16} and R^{17} are independently selected from the group consisting of

(a) hydrogen

(b) C_{1-6}alkyl,

(c) C_{1-6}alkanoic acid,

(d) C_{1-6}alkyl amine,

(e) phenyl or monosubstituted phenyl wherein the substituents are halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkanoic acid, C_{1-6}alkylamine, CN, CO_2H or CF_3, and

(f) benzyl or monosubstituted benzyl wherein the substituents are halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkanoic acid, C_{1-6}alkylamine, CN, CO_2H or CF_3.

Within this class there is a sub-class of compounds wherein

X is O;

Y is O;

R^1 is selected from the group consisting of
(a) SO_2CH_3, and
(b) $SO_2NR^{16}R^{17}$;

R^2 is selected from the group consisting of
mono- or di- substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of
(1) hydrogen,
(2) halo,
(5) CN,
(6) CF_3, and
(7) C_{1-4} alkyl,

R^3 is hydrogen or C_{1-3} alkyl;

R^4 is hydrogen or C_{1-3} alkyl;

R^9 and R^{10} together with the carbon to which they are connected form a carbonyl. R^{16} and R^{17} equal to hydrogen is preferred.

Within this sub-class there is a goup of compounds wherein

X is O;

Y is O;

R^1 is selected from the group consisting of
(a) SO_2CH_3, and
(b) $SO_2NR^{16}R^{17}$;

R^2 is selected from the group consisting of
mono- or di- substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of
(1) hydrogen,
(2) halo,
(5) CN,
(6) CF_3, and
(7) C_{1-4} alkyl,

R^3 is methyl or ethyl;

R^4 is methyl or ethyl; and

R^9 and R^{10} together with the carbon to which they are connected form a carbonyl.

Within the above embodiment there is another genus of compounds wherein

X is selected from the group consisting of

(a) CH_2, and

(b) O,

Y is selected from the group consisting of

(a) CH_2, and

(b) O,

R^1 is selected from the group consisting of

(a) SO_2CH_3,

(b) $SO_2NR^{16}R^{17}$, and

(c) $S(O)(NH)NH_2$;

R^2 is selected from the group consisting of

(a) mono- , di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or
the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, or 3 additional N atoms, wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C_{1-6}alkyl,

(4) C_{1-6}alkoxy,

(5) C_{1-6}alkylthio,

(6) CN,

(7) CF_3,

(8) $-C(R^5)(R^6)$-OH, and

(b) a mono- or di- substituted benzoheterocycle in which the heterocycle is a 5, 6, or 7-membered ring which may contain 1 or 2 heteroatoms chosen independently from O, S, or N and which may contain a carbonyl group or a sulfonyl group;

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wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkyl,
(4) C_{1-6}alkoxy,
(5) C_{1-10}alkylthio,
(6) CN,
(7) CF_3,
(8) $-C(R^5)(R^6)$-OH, and

(c) a heterocycloalkyl group of 5, 6 or 7 members which contains 1 or 2 heteroatoms chosen from O, S, or N and optionally contains a carbonyl group or a sulfonyl group.

(d) a mono- or di- substituted benzocarbocycle in which the carbocycle is a 5, 6, or 7-membered ring which optionally contains a carbonyl group, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkyl,
(4) C_{1-6}alkoxy,
(5) C_{1-6}alkylthio,
(6) CN,
(7) CF_3,
(8) $-C(R^5)(R^6)$-OH, and

(e) a mono- or di-substituted bicyclic heteroaryl of 8, 9, or 10 members, containing 2, 3, 4 or 5 heteroatoms chosen independently from O, S or N, and in which each ring contains at least one heteroatom, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkyl,
(4) C_{1-6}alkoxy,

(5) C_{1-6}alkylthio,
(6) CN,
(7) CF_3,
(8) $-C(R^5)(R^6)-OH$, and

R^3 is hydrogen, C_{1-6} alkyl, CH_2OR^7, CN, CH_2CN, C_{1-3}fluoroalkyl, F, $CON(R^7)_2$, mono- or di-substituted phenyl, mono or di-substituted benzyl, mono- or di-substituted heteroaryl, mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-4}alkyl,
(4) C_{1-4}alkoxy,
(5) C_{1-4}alkylthio,
(6) CN,
(7) CF_3,
(8) $-C(R^5)(R^6)-OH$, and

R^4 is

(a) hydrogen
(b) C_{1-4}alkyl,
(c) C_{1-4}alkoxy,
(d) C_{1-4}alkylthio,
(e) -OH,
(f) $-OCOR^7$,
(g) $-SCOR^7$,
(h) $-OCO_2R^8$, and
(i) $-SCO_2R^8$,

or R^3 andR^4 together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^5 and R^6 are each independently selected from the group consisting of

(a) hydrogen, and
(b) C_{1-4}alkyl,

or R^5 and R^6 together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6 or 7 atoms;

each R^7 is independently selected from the group consisting of

(a) hydrogen,

(b) C_{1-4}alkyl,

(c) phenyl or monosubstituted phenyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3, and

(d) benzyl or monosubstituted benzyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3

each R^8 is independently selected from the group consisting of

(a) C_{1-4}alkyl,

(b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3, and

(c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3;

R^9 and R^{10} together with the carbon to which they are connected form a carbonyl;

R^{16} and R^{17} are independently selected from the group consisting of

(a) hydrogen

(b) C_{1-6}alkyl,

(c) C_{1-6}alkanoic acid,

(d) C_{1-6}alkyl amine,

(e) phenyl or monosubstituted phenyl wherein the substituents are halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkanoic acid, C_{1-6}alkylamine, CN, CO_2H or CF_3, and

(f) benzyl or monosubstituted benzyl wherein the substituents are halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkanoic acid, C_{1-6}alkylamine, CN, CO_2H or CF_3.

Within this genus there is a class of compounds wherein

R^2 is a mono- or di-substituted heteroaryl wherein heteroaryl is selected from the group consisting of

(1) furanyl,
(2) diazinyl,
(3) imidazolyl,
(4) isooxazolyl,
(5) isothiazolyl,
(6) oxadiazolyl,
(7) oxazolyl,
(8) pyrazolyl,
(9) pyridyl,
(10) pyrrolyl,
(11) tetrazinyl
(12) tetrazolyl.
(13) thiadiazolyl,
(14) thiazolyl,
(15) thienyl,
(16) triazinyl, or
(17) triazolyl, and the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-4}alkyl,
(4) C_{1-4}alkoxy,
(5) C_{1-4}alkylthio,
(6) CN, and
(7) CF_3.

Within this class there is a sub-class of compounds wherein

X is O;
Y is O;
R^1 is selected from the group consisting of

(a) SO_2CH_3, and
(b) SO_2NH_2;

R^2 is a mono- or di-substituted heteroaryl wherein heteroaryl is selected from the group consisting of

(1) furanyl,
(2) diazinyl,
(3) imidazolyl,
(4) oxadiazolyl,
(5) pyrazolyl,
(6) pyridyl,
(7) pyrrolyl,
(8) thiazolyl,
(9) thienyl, wherein the substituents are selected from the group consisting of
  (1) hydrogen,
  (2) halo,
  (3) methyl,
  (4) methoxy, and
  (5) CF_3;

R^3 is hydrogen, C_{1-6} alkyl, CH_2OR^7, CN, CH_2CN, C_{1-4}fluoroalkyl, F, mono- or di-substituted phenyl, mono or di-substituted benzyl, mono- or di-substituted heteroaryl, mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-3}alkyl,
(4) C_{1-3}alkoxy,
(5) C_{1-3}alkylthio,
(6) CN, and
(7) CF_3;

R^4 is

(a) hydrogen
(b) C_{1-3}alkyl,
(c) C_{1-3}alkoxy,
(d) C_{1-3}alkylthio, and

(e) -OH; and

R^9 and R^{10} together with the carbon to which they are connected form a carbonyl.

Within this sub-class there is a group of compounds wherein

X is O;

Y is O;

R^1 is selected from the group consisting of

(a) SO_2CH_3, and

(b) SO_2NH_2;

R^2 is a mono- or di-substituted heteroaryl wherein heteroaryl is selected from the group consisting of

(1) furanyl,

(2) diazinyl,

(3) imidazolyl,

(4) oxadiazolyl,

(5) pyrazolyl,

(6) pyridyl,

(7) thiazolyl,

(8) thienyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) Cl or F,

(3) methyl,

(4) methoxy, and

(5) CF_3;

R^3 is hydrogen or C_{1-3} alkyl;

R^4 is hydrogen or C_{1-3} alkyl;

R^9 and R^{10} together with the carbon to which they are connected form a carbonyl.

Within the above embodiment there is another genus wherein

X is selected from the group consisting of

(a) CH_2, and

(b) O,

Y is selected from the group consisting of

(a) CH_2, and

(b) O,

R^1 is selected from the group consisting of

(a) SO_2CH_3,

(b) $SO_2NR^{16}R^{17}$, and

(c) $S(O)(NH)NH_2$;

R^2 is C_{1-6}alkyl,

R^3 is hydrogen, C_{1-6} alkyl, CH_2OR^7, CN, CH_2CN, C_{1-4}fluoroalkyl, F, $CON(R^7)_2$, mono- or di-substituted phenyl, mono or di-substituted benzyl, mono- or di-substituted heteroaryl, mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-4}alkyl,
(4) C_{1-4}alkoxy,
(5) C_{1-4}alkylthio,
(6) CN,
(7) CF_3,
(8) $-C(R^5)(R^6)-OH$, and

R^4 is

(a) hydrogen
(b) C_{1-6}alkyl,
(c) C_{1-6}alkoxy,
(d) C_{1-6}alkylthio,
(e) -OH,
(f) $-OCOR^7$,
(g) $-SCOR^7$,
(h) $-OCO_2R^8$, and
(i) $-SCO_2R^8$,

or R^3 andR^4 together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^5 and R^6 are each independently selected from the group consisting of

(a) hydrogen, and

(b) C_{1-6}alkyl,

or R^5 and R^6 together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6 or 7 atoms;

each R^7 is independently selected from the group consisting of

(a) hydrogen,

(b) C_{1-4}alkyl,

(c) phenyl or monosubstituted phenyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3, and

(d) benzyl or monosubstituted benzyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3

each R^8 is independently selected from the group consisting of

(a) C_{1-4}alkyl,

(b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3, and

(c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3;

R^9 and R^{10} together with the carbon to which they are connected form a carbonyl;

R^{16} and R^{17} are independently selected from the group consisting of

(a) hydrogen

(b) C_{1-6}alkyl,

(c) C_{1-6}alkanoic acid,

(d) C_{1-6}alkyl amine,

(e) phenyl or monosubstituted phenyl wherein the substituents are halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkanoic acid, C_{1-6}alkylamine, CN, CO_2H or CF_3, and

(f) benzyl or monosubstituted benzyl wherein the substituents are halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkanoic acid, C_{1-6}alkylamine, CN, CO_2H or CF_3.

Within this genus there is a sub-genus of compounds wherein

X is O;

Y is O;

R^1 is selected from the group consisting of

(a) SO_2CH_3,

(b) $S(O)_2NR^{16}R^{17}$, and

(c) $S(O)(NH)NH_2$;

R^2 is C_{1-4}alkyl,

R^3 is hydrogen, C_{1-6} alkyl, CH_2OR^7, CN, CH_2CN, C_{1-4}fluoroalkyl, F, $CON(R^7)_2$, mono- or di-substituted phenyl, mono or di-substituted benzyl, mono- or di-substituted heteroaryl, mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C_{1-4}alkyl,

(4) C_{1-4}alkoxy,

(5) C_{1-4}alkylthio,

(6) CN,

(7) CF_3,

(8) $-C(R^5)(R^6)-OH$, and

R^4 is

(a) hydrogen

(b) C_{1-6}alkyl,

(c) C_{1-6}alkoxy,

(d) C_{1-6}alkylthio,

(e) -OH,

(f) $-OCOR^7$,

(g) $-SCOR^7$,
(h) $-OCO_2R^8$, and
(i) $-SCO_2R^8$,

or R^3 andR^4 together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^5 and R^6 are each independently selected from the group consisting of
(a) hydrogen, and
(b) C_{1-6}alkyl,
or R^5 and R^6 together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6 or 7 atoms;

each R^7 is independently selected from the group consisting of
(a) hydrogen,
(b) C_{1-4}alkyl,
(c) phenyl or monosubstituted phenyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3, and
(d) benzyl or monosubstituted benzyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3

each R^8 is independently selected from the group consisting of
(a) C_{1-4}alkyl,
(b) phenyl or monosubstituted phenyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3, and
(c) benzyl or monosubstituted benzyl wherein the substituents may be halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, CN, or CF_3;

R^9 and R^{10} together with the carbon to which they are connected form a carbonyl;

R^{16} and R^{17} are independently selected from the group consisting of
(a) hydrogen
(b) C_{1-6}alkyl,
(c) C_{1-6}alkanoic acid,
(d) C_{1-6}alkyl amine,

(e) phenyl or monosubstituted phenyl wherein the substituents are halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkanoic acid, C_{1-6}alkylamine, CN, COOH or CF_3, and

(f) benzyl or monosubstituted benzyl wherein the substituents are halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkanoic acid, C_{1-6}alkylamine, CN, COOH or CF_3.

Within this sub-genus there is a class of compounds wherein

X is O;

Y is O;

R^1 is selected from the group consisting of

(a) SO_2CH_3, and

(b) $SO_2NR^{16}R^{17}$;

R^2 is propyl or butyl,

R^3 is hydrogen, C_{1-6} alkyl, CH_2OR^7, CN, CH_2CN, C_{1-4}fluoroalkyl, F, mono- or di-substituted phenyl, mono or di-substituted benzyl, mono- or di-substituted heteroaryl, mono or di-substituted heteroarylmethyl, wherein the substituents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-3}alkyl,
(4) C_{1-3}alkoxy,
(5) C_{1-3}alkylthio,
(6) CN, and
(7) CF_3;

R^4 is

(a) hydrogen
(b) C_{1-3}alkyl,
(c) C_{1-3}alkoxy,
(d) C_{1-3}alkylthio, and
(e) -OH; and

R^9 and R^{10} together with the carbon to which they are connected form a carbonyl. Preferred R^1 is SO_2CH_3 or R^1 is SO_2NH_2.

Within this class there is a sub-class of compounds wherein

X is O;

Y is O;

R^1 is selected from the group consisting of

(a) SO_2CH_3, and

(b) $SO_2NR^{16}R^{17}$;

R^2 is propyl or butyl,

R^3 is hydrogen or C_{1-3} alkyl;

R^4 is hydrogen or C_{1-3} alkyl;

R^9 and R^{10} together with the carbon to which they are connected form a carbonyl.

Within this sub-class there is a group of compounds wherein

X is O;

Y is O;

R^1 is selected from the group consisting of

(a) SO_2CH_3, and

(b) $SO_2NR^{16}R^{17}$;

R^2 is isopropyl,

R^3 is methyl or ethyl;

R^4 is methyl or ethyl; and

R^9 and R^{10} together with the carbon to which they are connected form a carbonyl.

For purposes of this specification heteroaryl as in R^2, R^3, or R^{15} is intended to include, but is not limited to optionally mono- or di-substituted

(1) furanyl,

(2) diazinyl,

(3) imidazolyl,

(4) isooxazolyl,

(5) isothiazolyl,

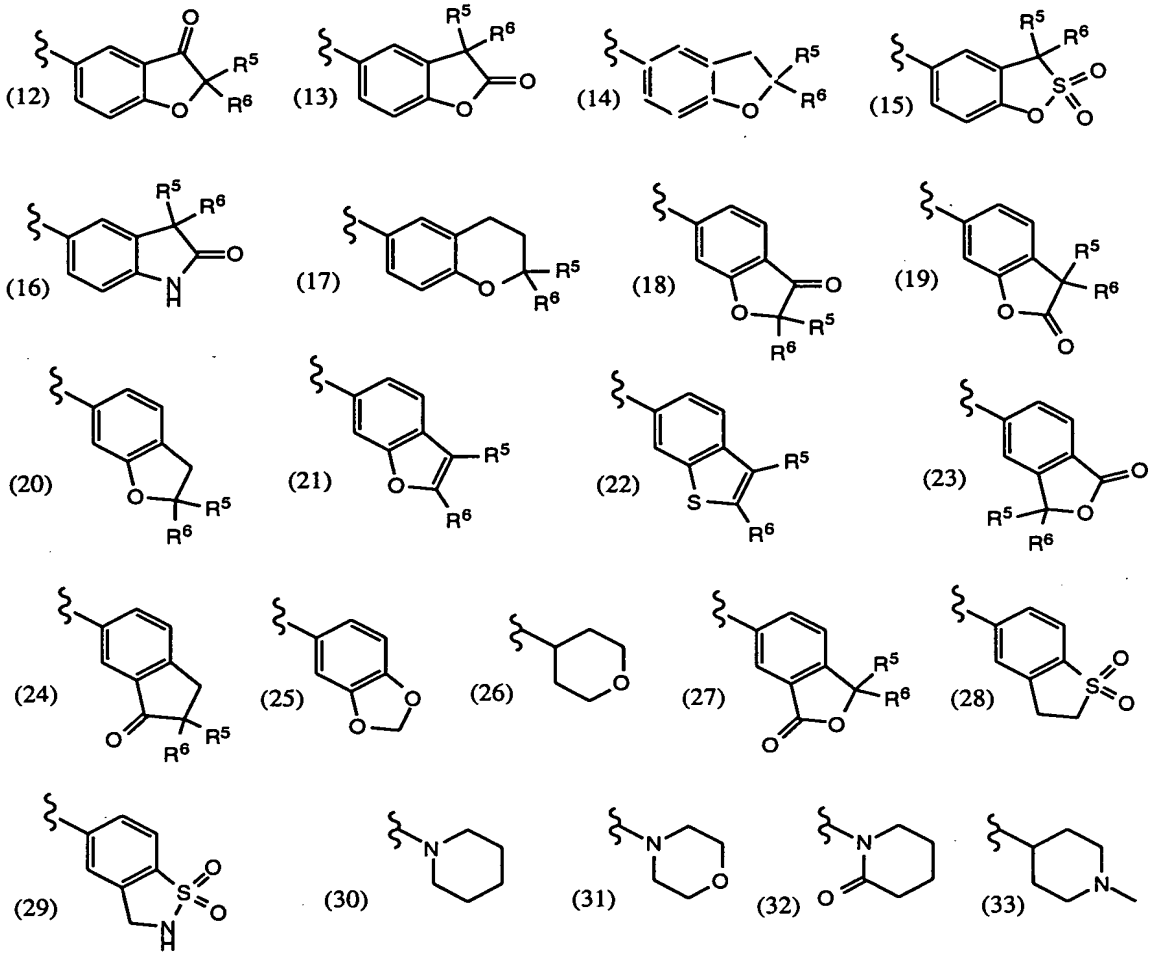
(6) oxadiazolyl,

(7) oxazolyl,
(8) pyrazolyl,
(9) pyridyl,
(10) pyrrolyl,
(11) tetrazinyl
(12) tetrazolyl.
(13) thiadiazolyl,
(14) thiazolyl,
(15) thienyl,
(16) triazinyl, or
(17) triazolyl.

Similarly, for purposes of this specification cyclic groups such as a heterocycloalkyl or benzocarbocycle or benzoheterocycle such as in R^2 or R^{15} is intended to include, but is not limited to optionally mono- or di-substituted

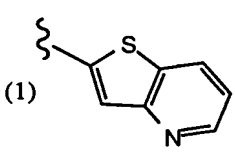
(1) tetrahydrothiopyranyl,
(2) thiomorpholinyl,
(3) pyrrolidinyl,
(4) hexahydroazepinyl,
(5) indanyl,
(6) tetralinyl,
(7) indolyl,
(8) benzofuranyl,
(9) benzothienyl,
(10) benzimidazolyl,
(11) benzothiazolyl,

T310X



Similarly, for purposes of this specification bicyclic heteroaryl as in R^2 is intended to include, but is not limited to optionally mono- or di-substituted

T320X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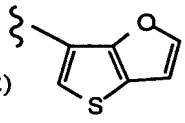
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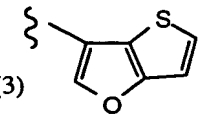
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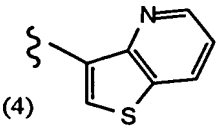
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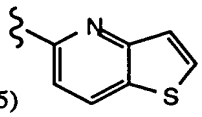
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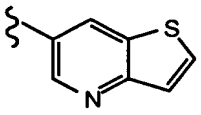
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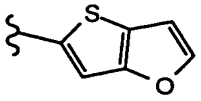
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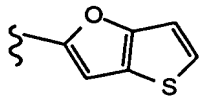
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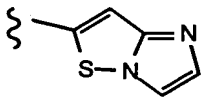
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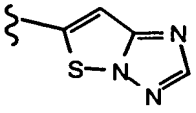
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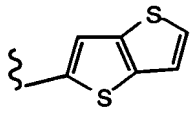
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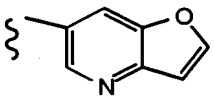
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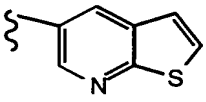
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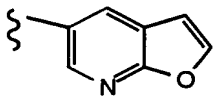
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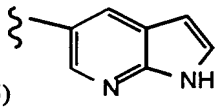
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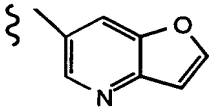
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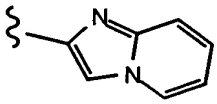
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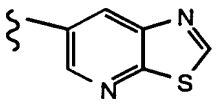
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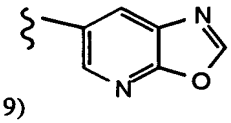
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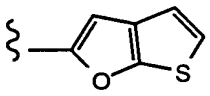
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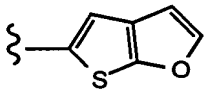

(21)

One preferred genus is directed to compounds of Formula I wherein R^9 and R^{10} together with the carbon atom to which they are attached form a carbonyl (ie R^9 and R^{10} together form a double bonded O).

Another preferred genus is directed to compounds of Formula I wherein Y is O.

Another preferred genus is directed to compounds of Formula I wherein X is O.

Another preferred genus is directed to compounds of Formula I wherein R^9 and R^{10} together with the carbon to which they are attached from a carbonyl;
Y is O; and
X is O.

Another preferred genus is directed to compounds of Formula I wherein
R^2 is a mono-, di- or tri-substituted phenyl wherein the substituents are selected from the group consisting of
(a) hydrogen,
(b) halo,
(c) CN,
(d) CF_3, and
(e) C_{1-4} alkyl.

Another preferred genus is directed to compounds of Formula I wherein
R^2 is mono-, di-, or tri-substituted pyridyl wherein the substituents are selected from the group consisting of
(a) hydrogen,
(b) halo,
(c) C_{1-4} alkyl,
(d) C_{1-4} alkoxy
(e) C_{1-4} alkythio,
(f) CN, and
(g) CF_3.

Another preferred genus is directed to compounds of Formula I wherein
R^9 and R^{10} together with the carbon to which they are attached from a carbonyl;
Y is O;
X is O, and

R^2 is a mono-, di- or tri-substituted phenyl wherein the substituents are selected from the group consisting of
(a) hydrogen,
(b) halo,
(c) CN,
(d) CF_3, and
(e) C_{1-4} alkyl.

Another preferred genus is directed to compounds of Formula I wherein
R^9 and R^{10} together with the carbon to which they are attached from a carbonyl,
Y is O,
X is O, and
R^2 is a mono-, di-, or tri-substituted pyridyl wherein the substituents are selected from the group consisting of
(a) hydrogen,
(b) halo,
(c) C_{1-4} alkyl,
(d) C_{1-4} alkoxy,
(e) C_{1-4} alkythio,
(f) CN, and
(g) CF_3.

Another preferred genus is directed to compounds of Formula I wherein
R^2 is a mono- or di-substituted phenyl, naphthyl, heteroaryl, benzoheterocycle, benzocarbocycle or bicyclic heteroaryl, wherein the substituents are selected from the group consisting of
(a) hydrogen,
(b) halo,
(d) C_{1-4} alkyl,
(e) C_{1-4} alkoxy,

(f) C_{1-4} alkythio,

(g) CN, and

(h) CF_3.

Another preferred genus is directed to compounds of Formula I wherein

R^9 and R^{10} together with the carbon to which they are attached from a carbonyl,and

Y is CH_2.

Another preferred genus is directed to compounds of Formula I wherein

R^3 is hydrogen or C_{1-10}alkyl, particularly a propyl or butyl.

Another preferred genus is directed to compounds of Formula I wherein

R^3 is substituted pyridine, particularly a 3-pyridine.

Another preferred genus is directed to compounds of Formula I wherein R^1 is methyl sulfonyl.

Another preferred genus is directed to compounds of formula I wherein R16 and R17 are each hydrogen.

In another aspect the invention also encompasses a pharmaceutical composition for treating an inflammatory disease susceptable to treatment with an non-steroidal anti-inflammatory agent comprising:

a non-toxic therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

In another aspect the invention also encompasses a pharmaceutical composition for treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:

a non-toxic therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

In another aspect the invention also encompasses a method of treating an inflammatory disease susceptable to treatment with an non-steroidal anti-inflammatory agent comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

In another aspect the invention also encompasses a method of treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of formula I.

In another aspect the invention also encompasses the use of a compound of formula I or a pharmaceutical composition in the manufacture of a medicament for the treatment of an inflammatory disease susceptable to treatment with an a non-steroidal anti-inflammatory agent.

The invention is illustrated by the compounds of the Examples disclosed herein as well as the compounds of Table I.

1) Definitions

The following abbreviations have the indicated meanings:

AA	=	arachidonic acid
Ac	=	acetyl
AIBN	=	2.2--azobisisobutyronitrile
Bn	=	benzyl
CHO	=	chinese hamster ovary
CMC	=	1-cyclohexyl-3-(2-morpholinoethyl) carbodiimidemetho-*p*-toluenesulfonate
COX	=	cyclooxygenase
DBU	=	diazabicyclo[5.4.0]undec-7-ene

DMAP	=	4-(dimethylamino)pyridine
DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulfoxide
Et_3N	=	triethylamine
HBSS	=	Hanks balanced salt solution
HEPES	=	N-[2-Hydroxyethyl]piperazine-N^1-[2-ethanesulfonic acid]
HWB	=	human whole blood
IPA	=	isopropyl alcohol
KHMDS	=	potassium hexamethyldisilazane
LDA	=	lithium diisopropylamide
LPS	=	lipopolysaccharide
mCPBA	=	metachloro perbenzoic acid
MMPP	=	magnesium monoperoxyphthalate
Ms	=	methanesulfonyl = mesyl
Ms0	=	methanesulfonate = mesylate
NBS	=	N-bromosuccinimide
NCS	=	N-chlorosuccinimide
NIS	=	N-iodosuccinimide
NSAID	=	non-steroidal anti-inflammatory drug
ODCB	=	o-dichlorobenzene
Oxone®	=	potassium peroxymonosulfate
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
r.t.	=	room temperature
rac.	=	racemic
Tf	=	trifluoromethanesulfonyl = triflyl
TFAA	=	trifluoroacetic anhydride
Tf0	=	trifluoromethanesulfonate = triflate
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
TMPD	=	N,N,N',N'-tetramethyl-p-phenylenediamine
Ts	=	p-toluenesulfonyl = tosyl
TsO	=	p-toluenesulfonate = tosylate

Tz	=	1H (or 2H)-tetrazol-5-yl
SO_2Me	=	methyl sulfone (also SO_2CH_3)
SO_2NH_2	=	sulfonamide

T380X

Alkyl group abbreviations

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

Dose Abbreviations

bid = bis in die = twice daily
qid = quater in die = four times a day
id = ter in die = three times a day

For purposes of this specification "Alkyl" means linear branched and cyclic structures, and combinations thereof, containing the indicated number of carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, eicosyl, 3,7-diethyl-2,2-dimethyl- 4-propylnonyl, cyclopropyl, cyclopentyl, cycloheptyl, adamantyl, cyclododecylmethyl, 2-ethyl-1-bicyclo[4.4.0]decyl and the like.

For purposes of this specification "Fluoro alkyl" means alkyl groups in which one or more hydrogen is replaced by fluorine. Examples are $-CF_3$, $-CH_2CH_2F$, $-CH_2CF_3$, c-Pr-F5, c-Hex-F_{11} and the like.

For purposes of this specification "Alkoxy" means alkoxy groups of the indicated number of carbon atoms of a straight, branched, or cyclic configuration. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

For purposes of this specification "Alkylthio" means alkylthio groups of the indicated number of carbon atoms of a straight, branched or cyclic configuration. Examples of alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies $-SCH_2CH_2CH_3$.

For purposes of this specification "Halo" means F, Cl, Br, or I.

Exemplifying the invention are Examples hereinunder which include:

(1) 3-(3,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(2) 3-(3-Fluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)- 5H-furan-2-one,

(3) 3-(3,5-Difluorophenoxy)-5,5-dimethyl-4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(4) 3-Phenoxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(5) 3-(2,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(6) 3-(4-Chlorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(7) 3-(3,4-Dichlorophenoxy)-5,5-dimethyl-4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(8) 3-(4-Fluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(9) 3-(4-Fluorophenylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(10) 3-(3,5-Difluorophenylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(11) 3-Phenylthio-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,

(12) 3-(N-Phenylamino)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,

(13) 3-(N-Methyl-N-phenylamino)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
(14) 3-Cyclohexyloxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
(15) 3-Phenylthio-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
(16) 3-Benzyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
(17) 3-(3,4-Difluorophenylhydroxymethyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
(18) 3-(3,4-Difluorobenzoyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
(19) 3-Benzoyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
(20) 4-(4-(Methylsulfonyl)phenyl)-3-phenoxy-1-oxaspiro[4.4]non-3-en-2-one,
(21) 4-(4-(Methylsulfonyl)phenyl)-3-phenylthio-1-oxaspiro[4.4]non-3-en-2-one,
(22) 4-(2-Oxo-3-phenylthio-1-oxa-spiro[4,4]non-3-en-4-yl) benzenesulfonamide,
(23) 3-(4-Fluorobenzyl)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,
(24) 3-(3,4-Difluorophenoxy)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
(25) 3-(5-Chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
(26) 3-(2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
(27) 3-(6-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one,
(28) 3-(3-Isoquinolinoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one,
(29) 3-(4-(Methylsulfonyl)phenyl)-2-phenoxycyclopent-2-enone, and
(30) 3-(4-(Methylsulfonyl)phenyl)-2-(3,4-difluorophenoxy) cyclopent-2-enone.

Further exemplifying the invention are
(a) 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(5-bromopyridin-2-yloxy)-5H-furan-2-one, and
(b) 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one, or
a pharmaceutically acceptable salt thereof.

Also see Examples 1-205.

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

In a second embodiment, the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

Within this embodiment the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase-2 and for treating cyclooxygenase-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

In a third embodiment, the invention encompasses a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases, advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 as disclosed herein comprising:

administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like, and basic ion exchange resins.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The compound of Formula I is useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis),

gout and ankylosing spondylitis, bursitis, burns, injuries, following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastic tumor growth and hence can be used in the treatment of cancer. Compound I may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumour angiogenesis.

Compound I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, and for the prevention of bone loss (treatment of osteoporosis) and for the treatment of glaucoma.

By virtue of its high cyclooxygenase-2 (COX-2) activity and/or its specificity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1), Compound I will prove useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Similarly, Compound I, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetominophen or phenacetin; a potentiator including caffeine; an H_2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline,

ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a prostaglandin including misoprostol, enprostil, rioprostil, ornoprostol or rosaprostol; a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effective amount of the compound of Formula I, optionally co-administered with one or more of such ingredients as listed immediately above.

For the treatment of any of these cyclooxygenase mediated diseases Compound I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets.

These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one

or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxy-ethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have

been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compound I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans

may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

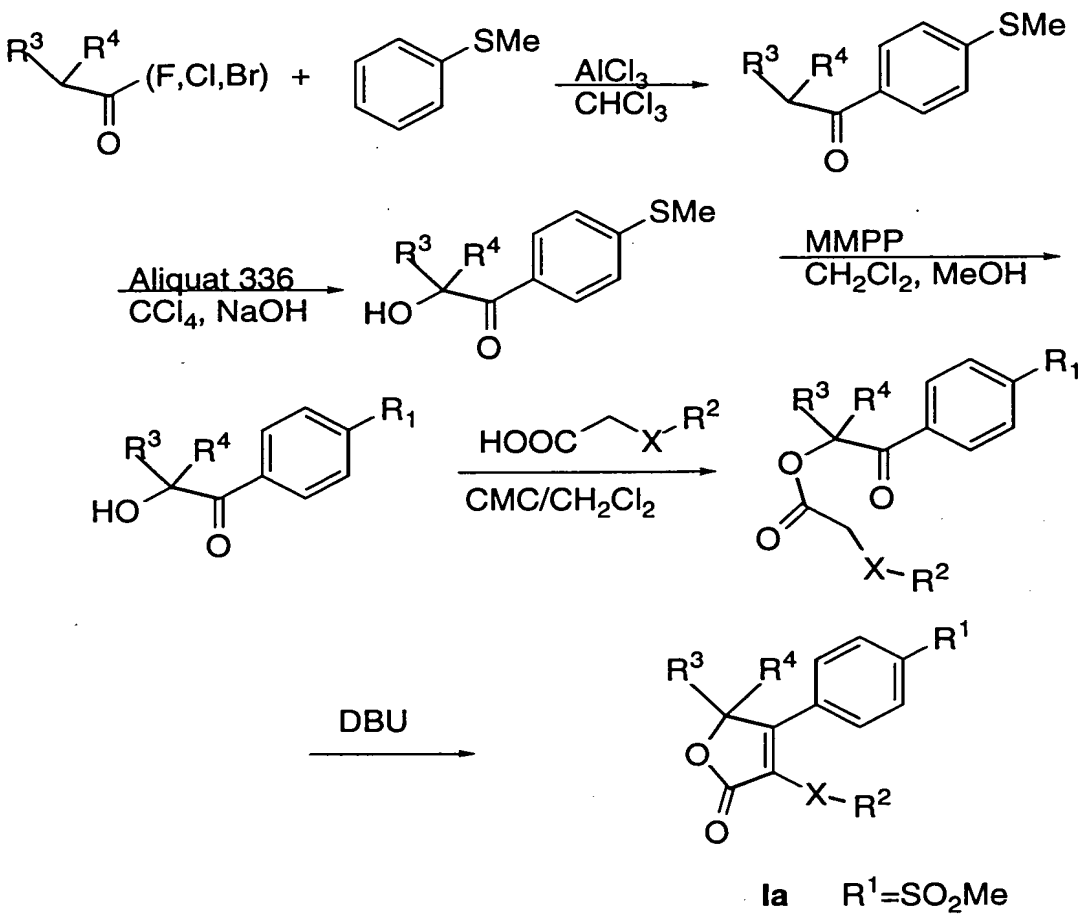
It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the present invention can be prepared according to the following methods

Method A

An appropriately substituted acid halide is reacted with thioanisole in a solvent such as chloroform in the presence of a Lewis acid such as aluminum chloride to afford a ketone which is then hydroxylated with base such as aqueous sodium hydroxide in a solvent such as carbon tetrachloride with a phase transfer agent such as Aliquat 336. Then treatment with an oxidizing agent such as MMPP in solvents such as CH_2Cl_2/MeOH, affords an sulfone which is reacted with an appropriately substituted acetic acid in a solvent such as CH_2Cl_2 in the presence of an esterifying agent such as CMC and DMAP and then treated with DBU to afford lactone **Ia**.

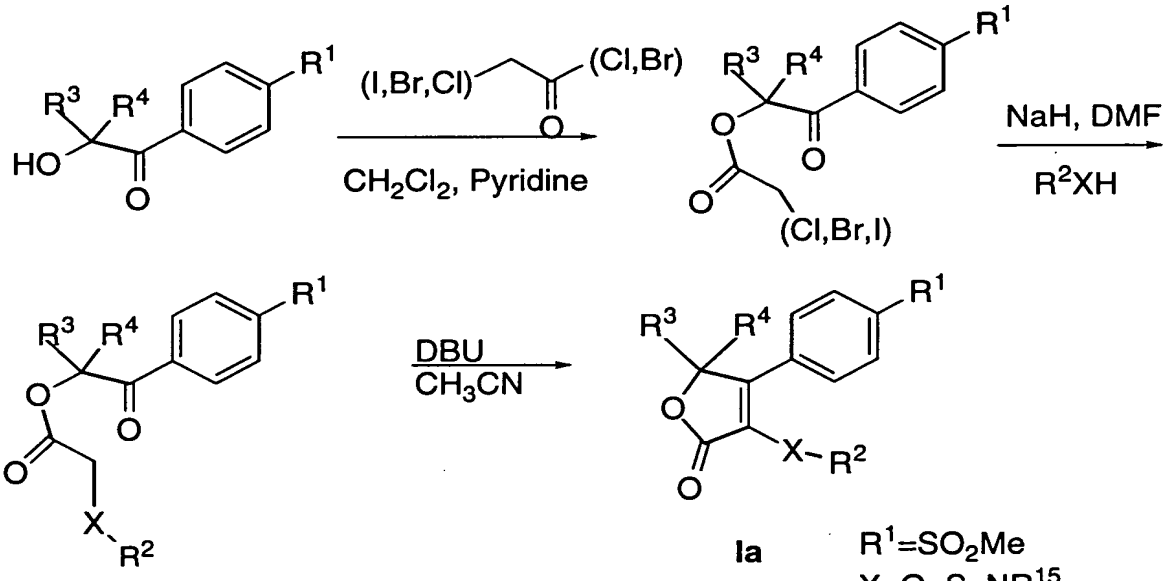
T490X



Ia $R^1=SO_2Me$

Method B

An appropriately substituted hydroxyketone is acylated withn appropriately substituted acid halide in a solvent such as dichloromethane in the presence of a base such as pyridine. The ester obtained is then reacted with an appropriately substituted nucleophile R^2XH in a solvent such as DMF and with a base such as sodium hydride, then treatment with DBU in a solvent such as acetonitrile affords lactone **Ia**.



Ia

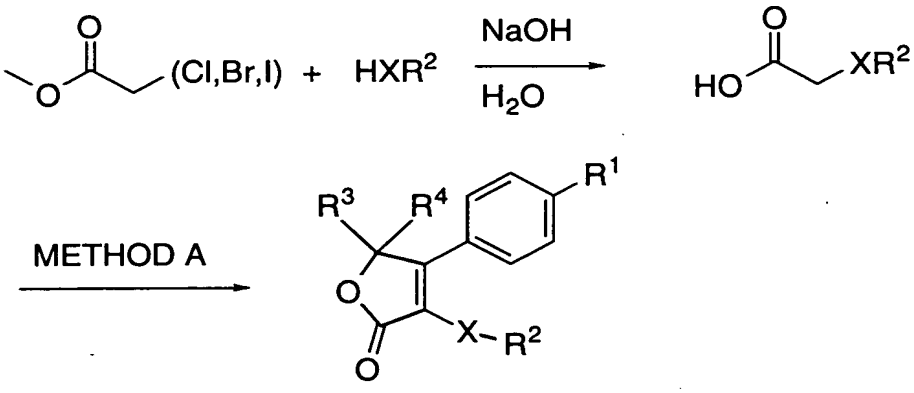
R^1=SO_2Me

X=O, S, NR^{15}

Method C

A halo ester of acetic acid is coupled with an appropriately substituted nucleophile in water with sodium hydroxide to give an appropriately substituted acetic acid which is then reacted as in method A to afford lactone **Ia**.

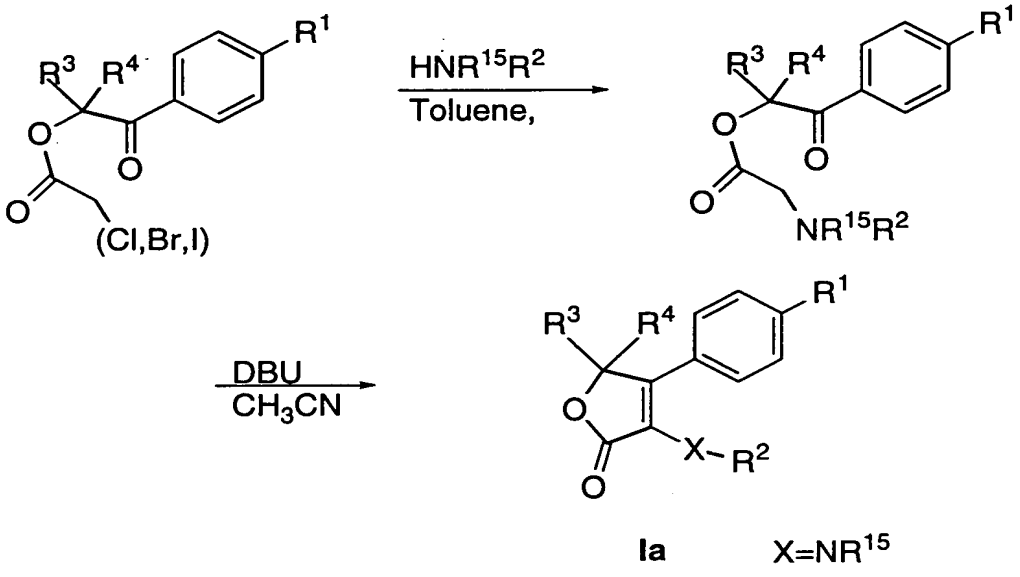
T570X



Ia $R^1=SO_2Me$
X=O, S, NR^{15}

Method D

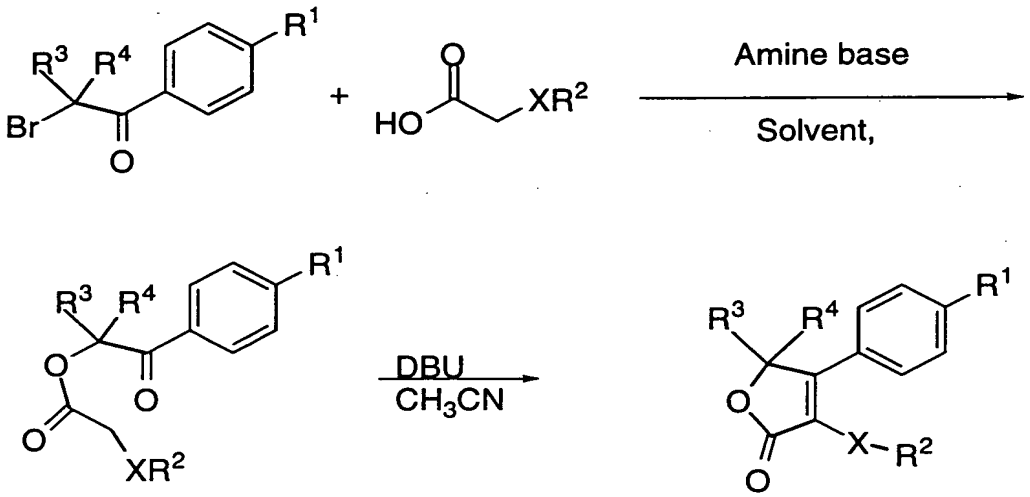
A halo ester is reacted with an appropriately substituted amine $R^2R^{15}NH$ in a solvent such as toluene to give an intermediate which is then reacted with DBU in a solvent such as acetonitrile to afford lactone **Ia**.



Ia X=NR15

Method E

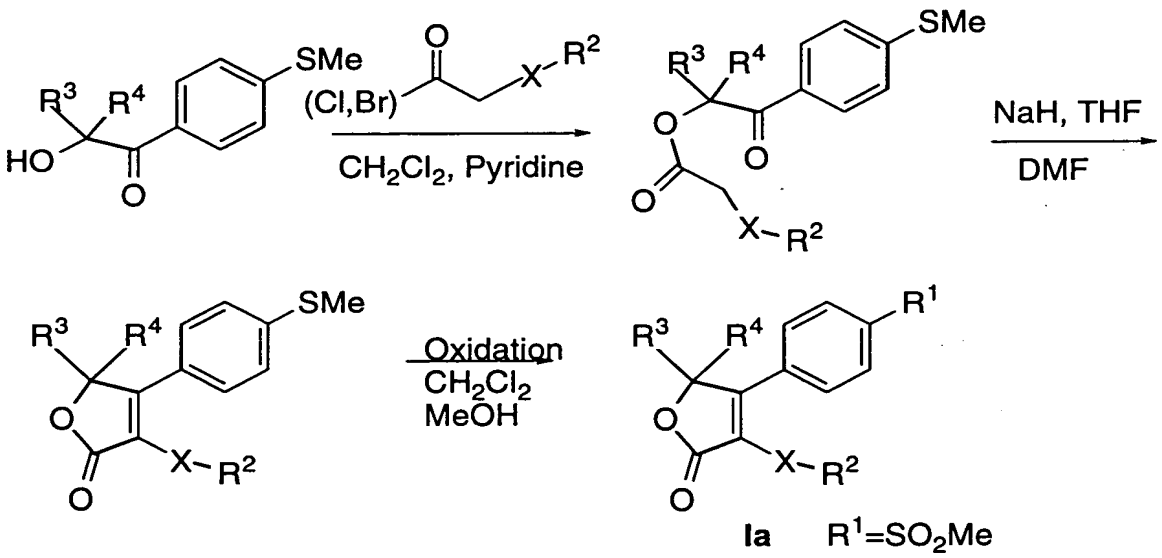
An appropriately substituted bromoketone is reacted with an appropriately substituted acid in a solvent such as ethanol or acetonitrile in the presence of a base such as diisopropylethylamine or triethylamine to afford an ester which is then treated with DBU in a solvent such as acetonitrile to afford lactone **Ia.**



Ia

Method F

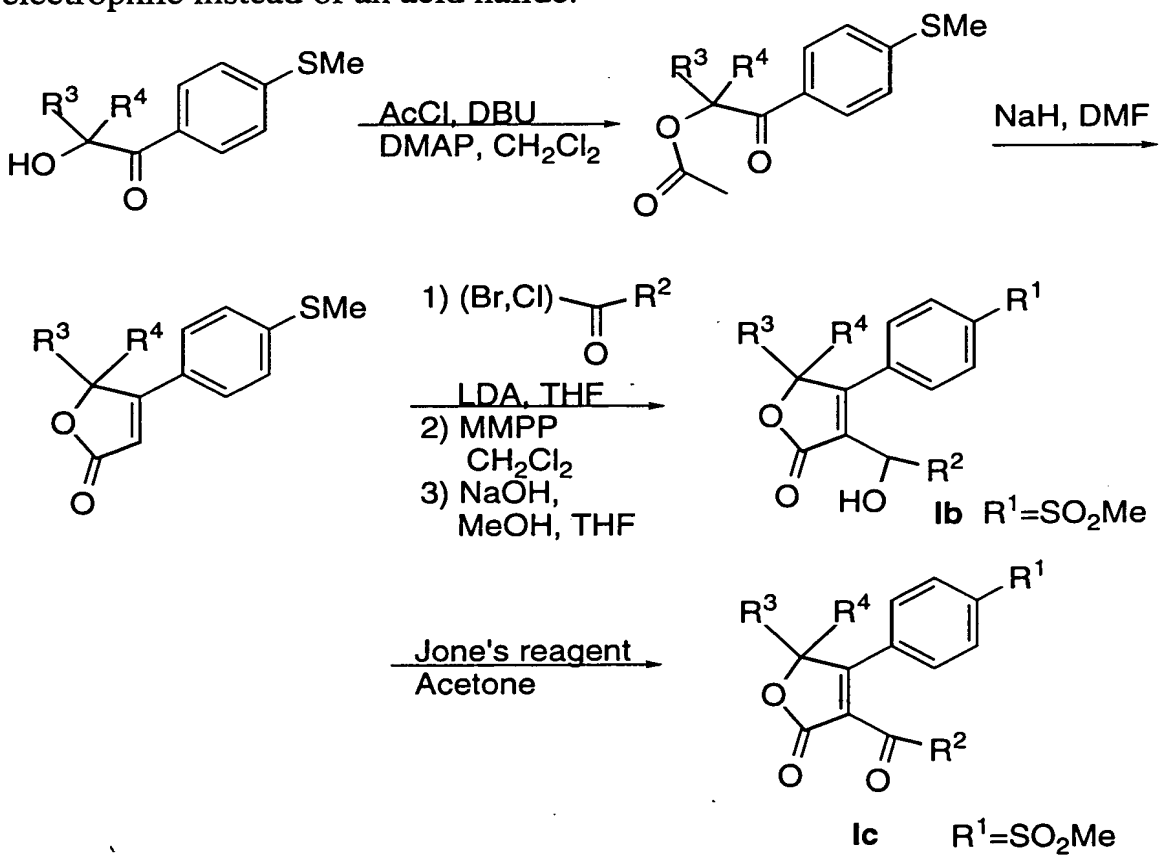
An appropriately substituted hydroxyketone is reacted with an appropriately substituted acid halide in a solvent such as dichloromethane and with a base such as pyridine to afford an ester which is then cyclized using sodium hydride in a mixture of THF and DMF to afford a lactone. The lactone is then oxidized with an oxidizing agent such as MMPP, mCPBA or OXONE® in solvents such as dichloromethane and/or methanol to afford lactone **Ia**.



Ia $R^1=SO_2Me$

Method G

An appropriately substituted hydroxyketone is acylated with acetyl bromide or chloride in a solvent such as dichloromethane with a base such as DBU and DMAP. Further treatment with a base such as sodium hydride in a solvent such as DMF effects cyclization to afford the 5-membered lactone. Treatment of this lactone with a base such as LDA and an appropriately substituted acid halide in a solvent such as THF, followed by oxidation with a reagent such as MMPP in solvent such as CH_2Cl_2/MeOH and hydrolysis by a base such as NaOH in a solvent such as MeOH/THF gives an alcohol **Ib** which is then oxidized to lactone **Ic** by a reagent such as Jone's reagent in a solvent such as acetone(the initially formed ketone is reduced in the reaction and acylated, thus requiring hydrolysis and re-oxidation to obtain ketone **Ic**). Alternatively, alcohol **Ib** can be obtained by using an aldehyde R^2CHO as the electrophile instead of an acid halide.

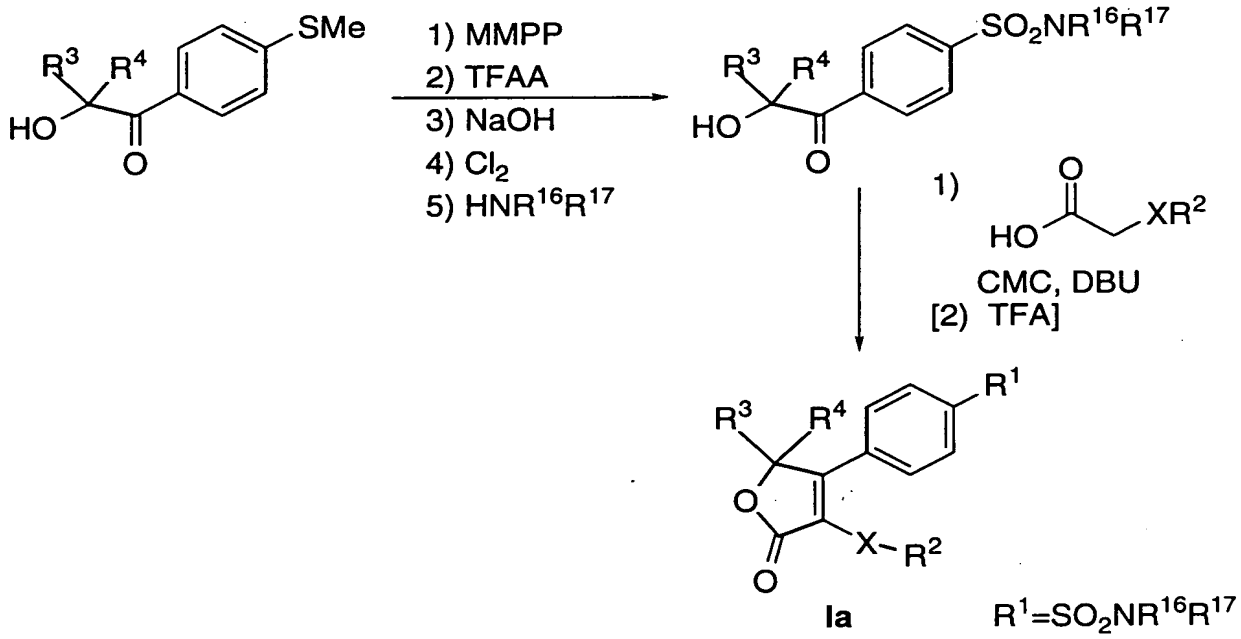


7550X

55

Method H

An appropriately substituted methyl sulfide is oxidized to the sulfoxide with a reagent such as MMPP in solvents such as dichloromethane and methanol followed by treatment with trifluoroacetic anhydride, then aqueous sodium hydroxide. Further treatment by Cl_2 in aqueous acetic acid followed by treatment by an amine affords an intermediate sulfonamide. This sulfonamide is then esterified with an appropriately substituted acid in the presence of a reagent such as CMC and further treatment with a base such as DBU affords the lactone. In the case where the amine group is protected by an acid labile group treatment with an acid such as trifluoroacetic acid in a solvent such as dichloromethane affords compound **Ia**.

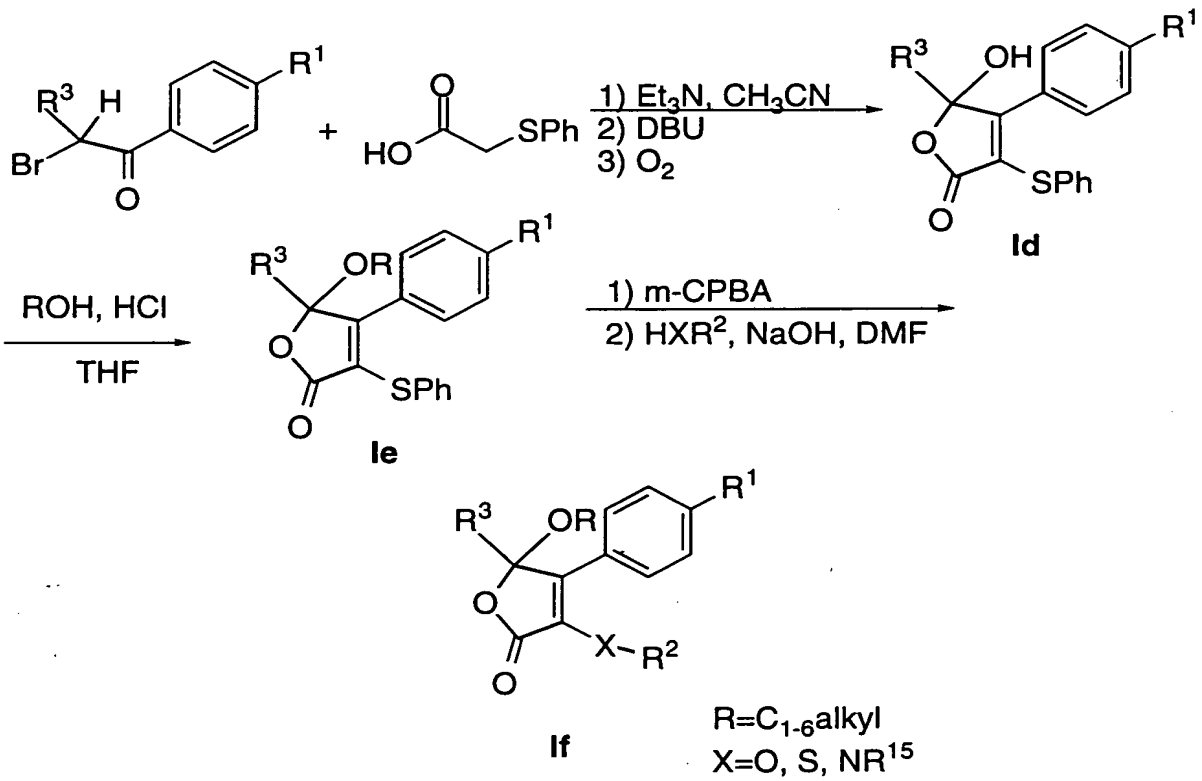


Ia $R^1=SO_2NR^{16}R^{17}$

T560X

Method I

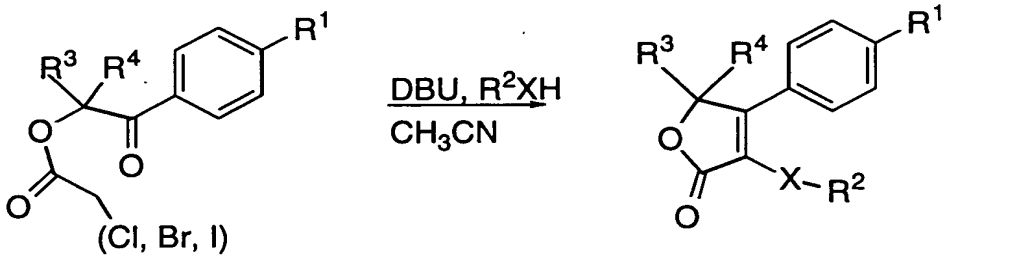
An appropriately substituted bromoketone is reacted with an appropriately substituted acid in a solvent such as acetonitrile and with a base such as Et3N. Treatment with DBUand then O_2 gives a hydroxy compound **Id**. Etherification of this hydroxy with an alcohol in a solvent such as THF and with an acid such HCl gives **Ie.** By oxidation of the sulfide into a sulfone by a reagent such as m-CPBA and then displacement of this sulfone by an appropriately substituted nucleophile compound **If** is obtained.



T570X

Method J

An appropriately substituted nucleophile is reacted with an appropriately substituted haloacetate in a solvent such as acetonitrile with a base such as DBU to afford compound **Ia.**



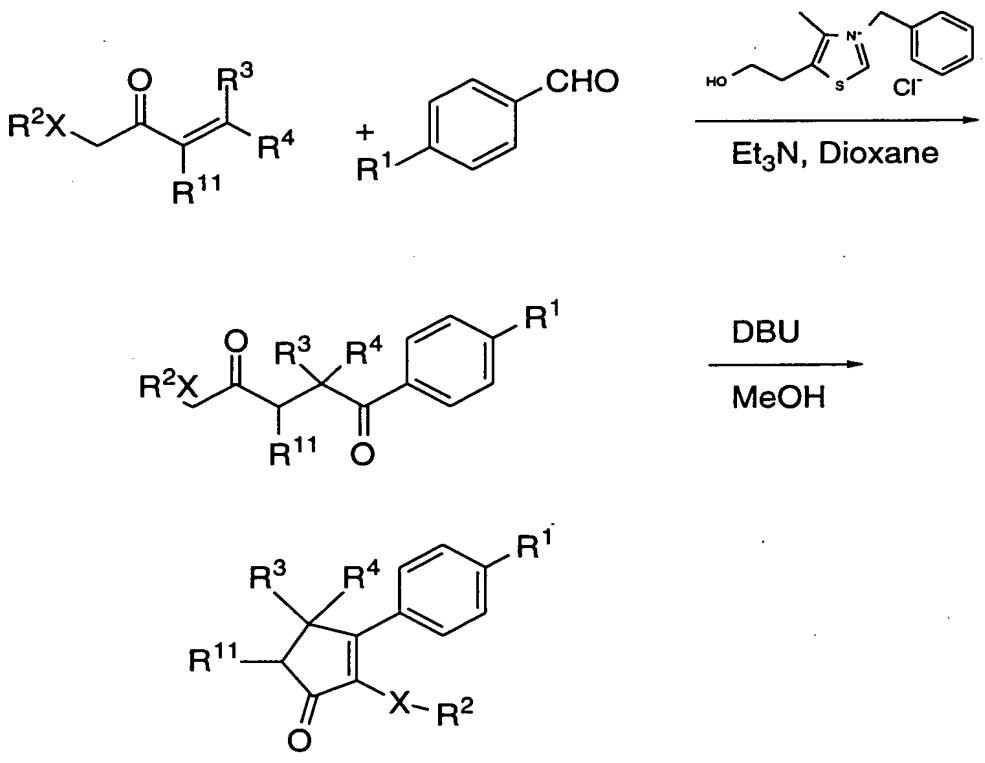
Ia X=O, S, NR^{15}

T580X

58

Method K

An appropriately substituted vinyl ketone is coupled with an appropriately substituted benzaldehyde with a catalyst such as 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride in the presence of a base such as triethylamine in a solvent such as 1,4-dioxane to form a diketone. The diketone is cyclized in a solvent such as methanol with a base such as DBU to the final product **Ig**. When R^1=SO_2Me, the starting material can also be a p-methylthiobenzaldehyde, with the methylthio group being oxidized to SO_2Me using MMPP, mCPBA or OXONE® in the last step.

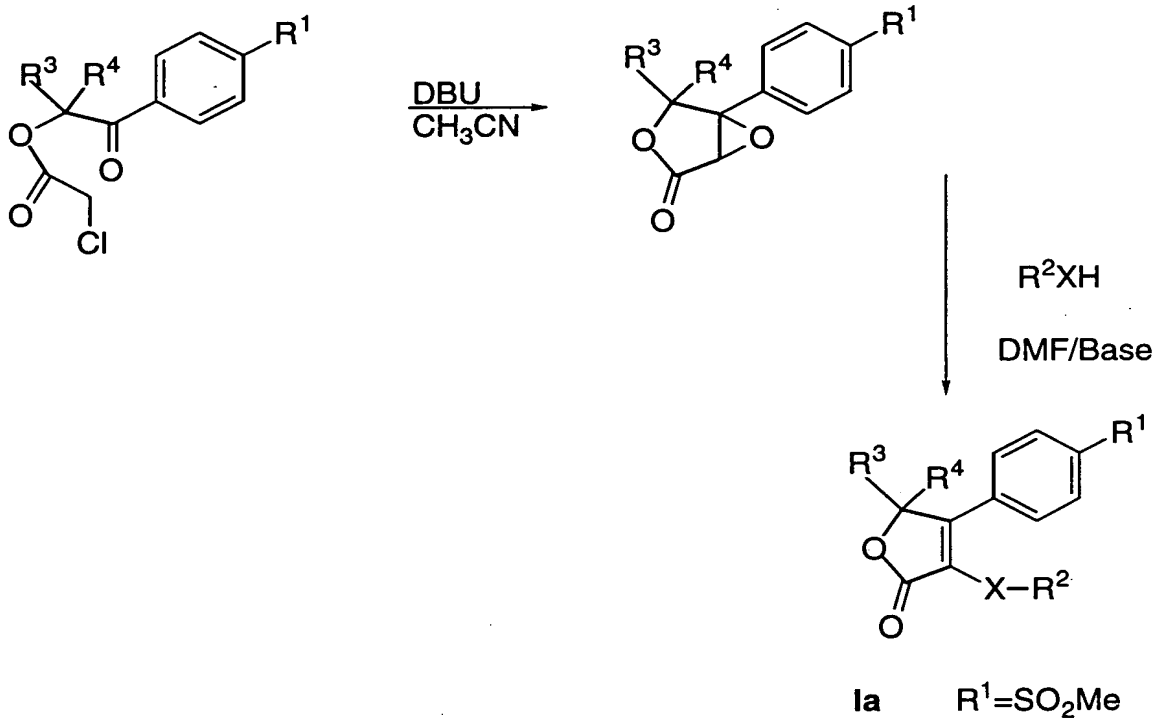


Ig

T590X

Method L

An appropriately substituted halide is reacted with a base such as DBU in a solvent such as acetonitrile to afford an epoxide which is then reacted with an appropriately substituted nucleophile in solvents such as DMF and a base to afford lactone **Ia**.

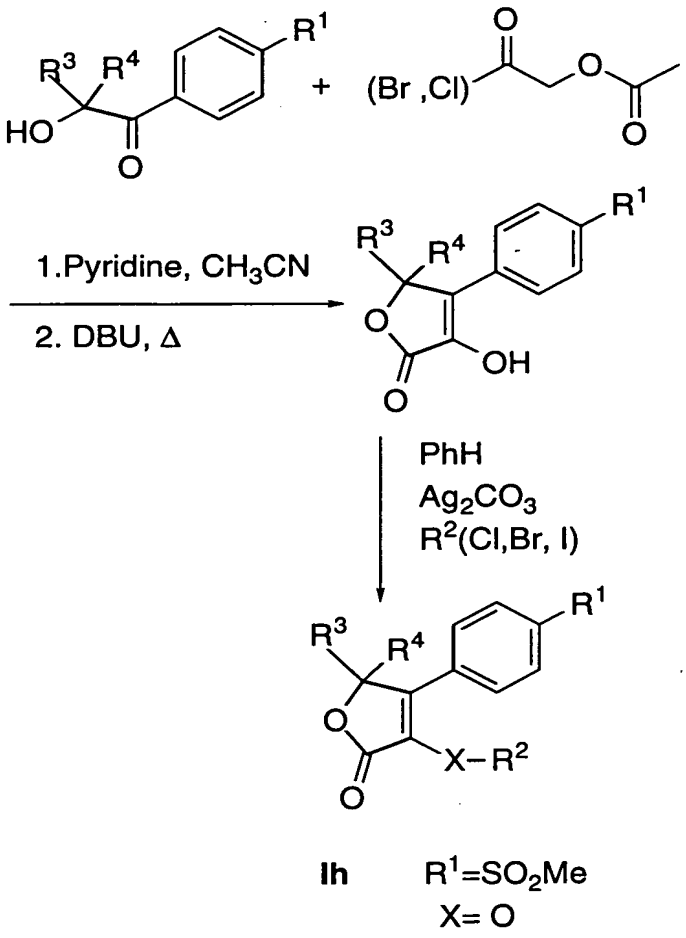


Ia $R^1=SO_2Me$

Method M

An appropriately substituted acid halide is reacted with an appropriately substituted hydroxyketone in the presence of a base such as pyridine in a solvent such as acetonitrile, further treatment with a base such as DBU gives an hydroxylactone. The hydroxylactone is reacted with an appropriately substituted halide in a solvent such as benzene with a reagent such as Ag_2CO_3 to afford the lactone **Ih**.

T610X

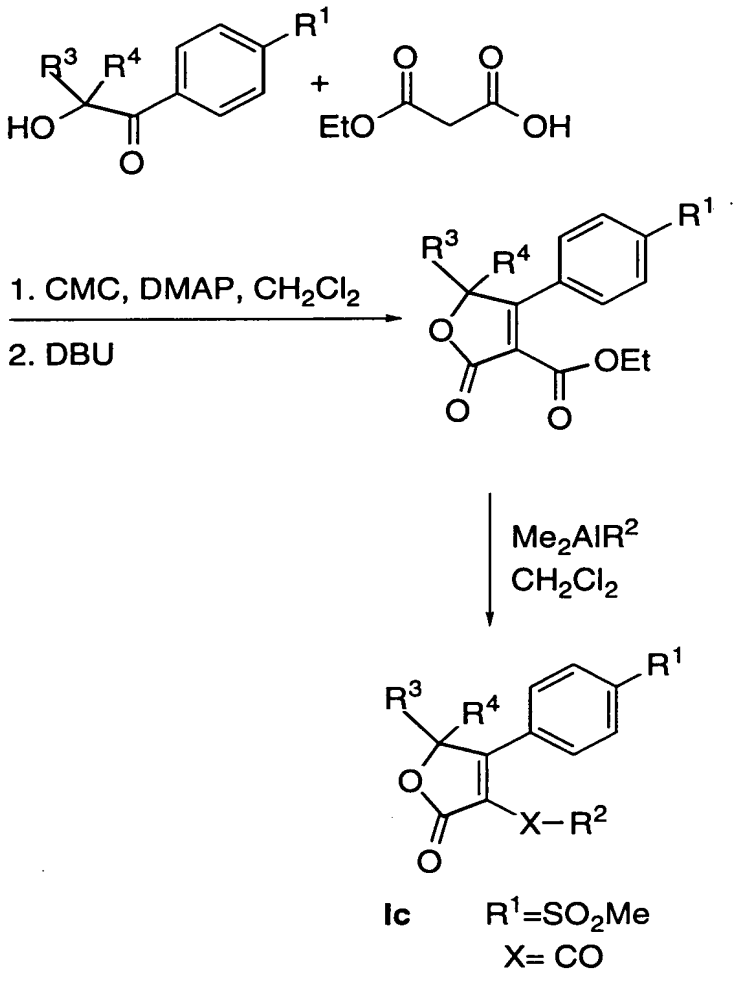


Ih R^1=SO_2Me
X= O

Method N

An appropriately substituted hydroxyketone is reacted with an appropriately substituted carboxylic acid with an esterifying agent such as CMC in the presence of DMAP in a solvent such CH_2Cl_2, followed by treatment with a base such as DBU to afford a lactone ester. This lactone ester is then reacted with a reagent such as the one formed with piperidine and trimethylaluminium to afford the lactone **Ic**.

T620X

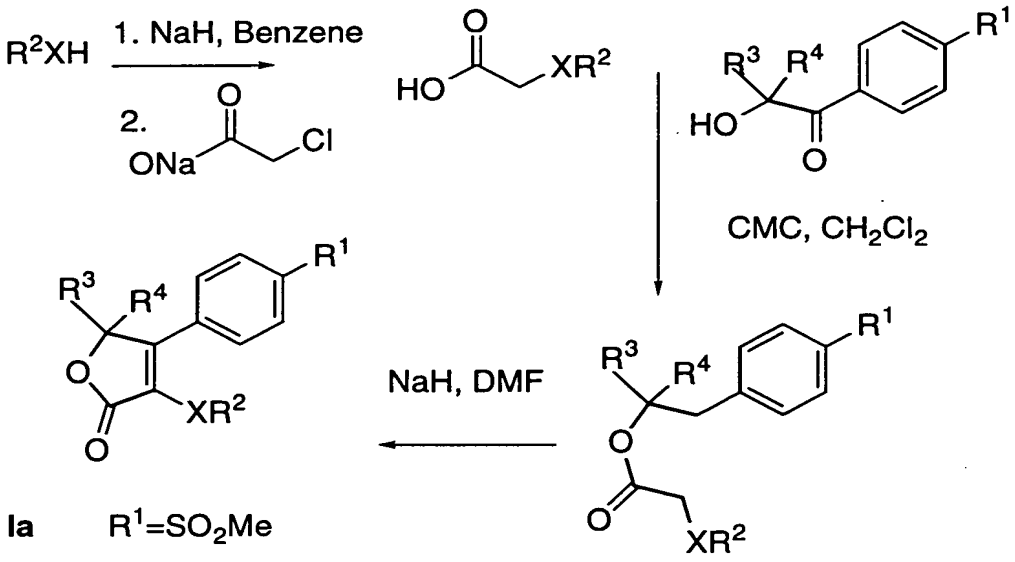


Ic R^1=SO_2Me
X= CO

Method O

An appropriately substituted nucleophile such as pentan-3-ol is treated with a base such as sodium hydride in a solvent such as benzene and then reacted with an electrophile such as sodium chloroacetate to afford an acid. This acid is then reacted with an appropriately substituted hydroxyketone with an esterifying reagent such as CMC in a solvent such as dichloromethane to give an ester which is cyclized upon treatment with a base such as sodium hydride in a solvent such as DMF to afford lactone **Ia**.

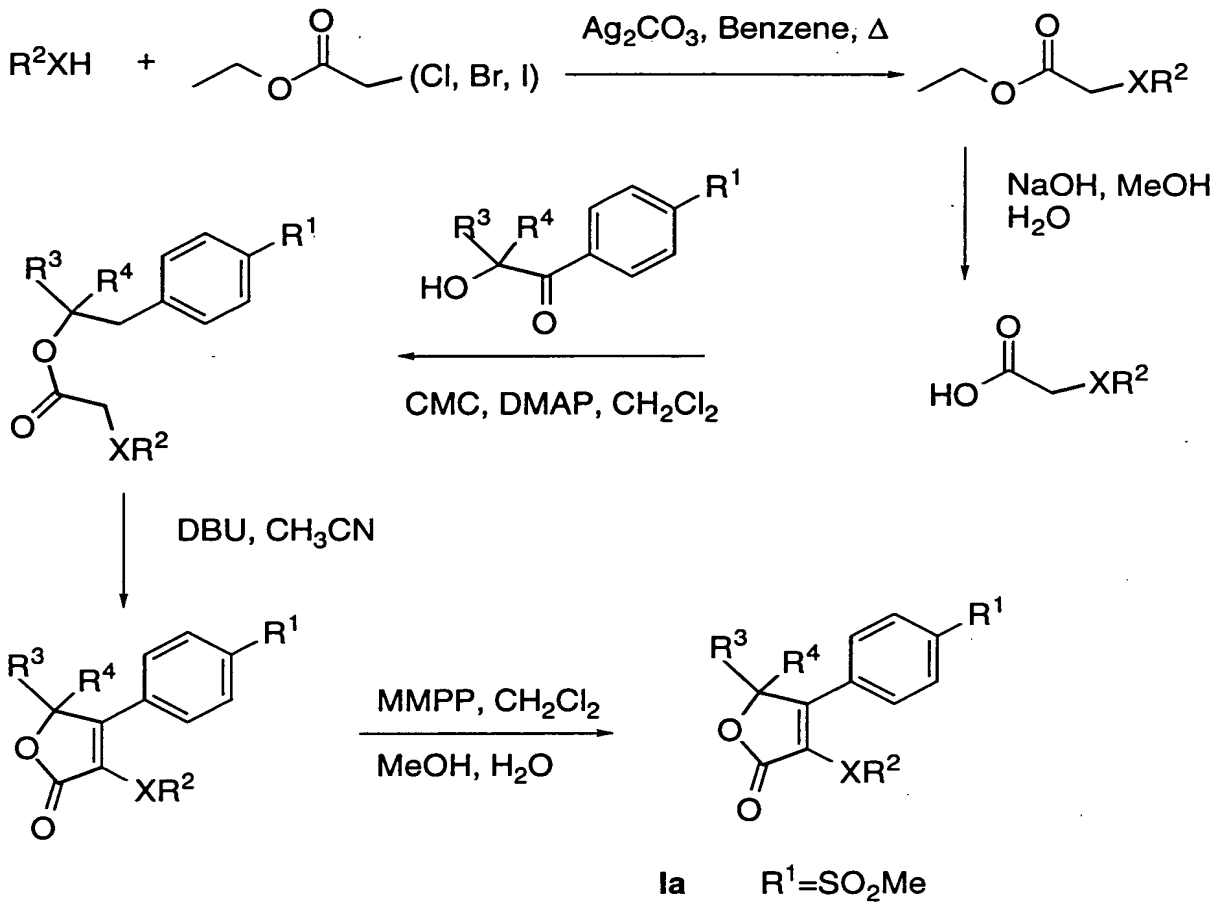
T630X



Method P

An appropriately substituted nucleophile is reacted with an appropriately substituted haloacetate alkaline salt (such as sodium) in a solvent such as benzene and with a reagent such as Ag_2CO_3 to give an ester which is then hydrolyzed with a reagent such as NaOH in solvents such as water and methanol to give an acid. The acid is then esterified with an appropriately substituted hydroxyketone with reagents such as CMC and DMAP in a solvent such as dichloromethane to give an ester which is then cyclized with a base such as DBU in a solvent such as CH_3CN to afford a lactone. The sulfide is then oxidized with a reagent such as MMPP in solvents such as CH_2Cl_2, MeOH and water to afford lactone **Ia**.

T640X

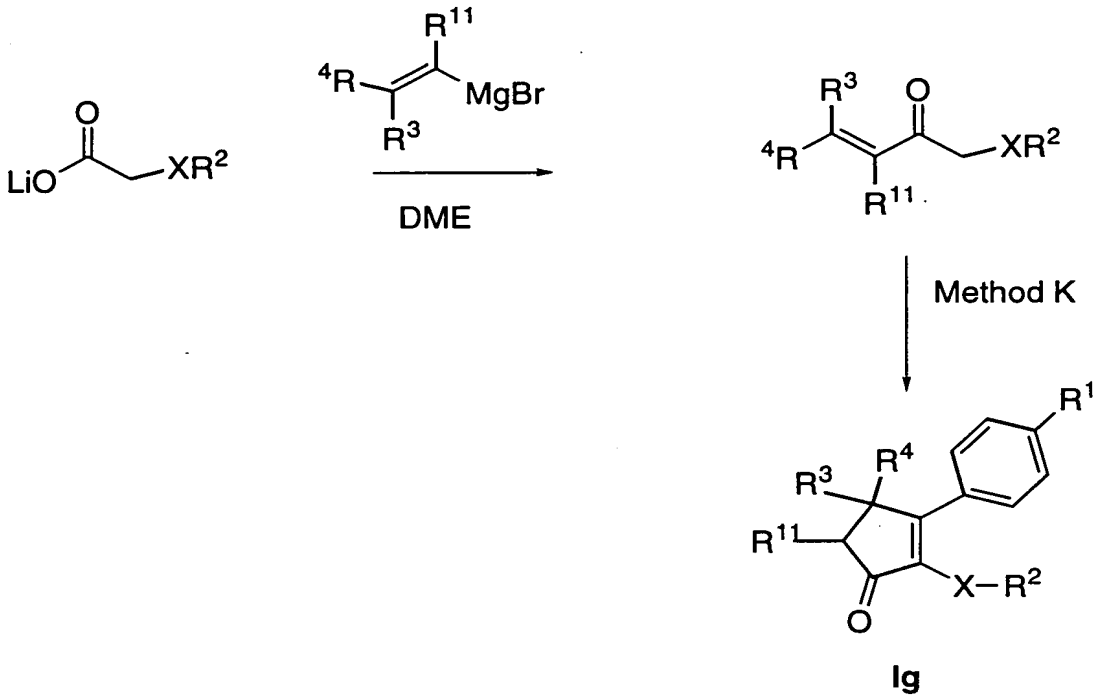


Ia $R^1=SO_2Me$

Method Q

An appropriately substituted acetic acid salt is reacted with a nucleophile such as vinyl magnesium bromide in a solvent such as DME to afford a ketone, which is then reacted as in method K to afford cyclopentone **Ig**.

7650X

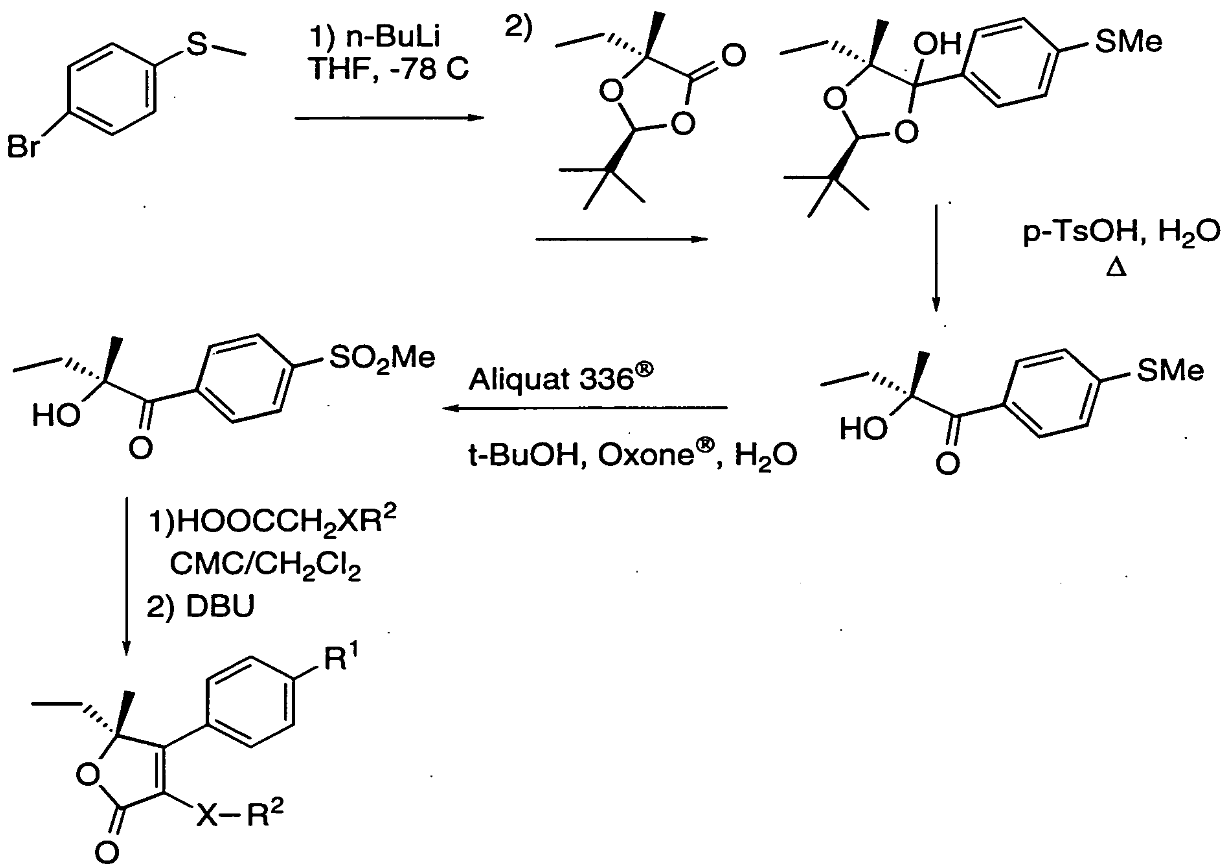


Ig

Method R

4-Bromothioanisole is reacted with a base such as n-BuLi in a solvent such as THF to form the corresponding lithium reagent which is then reacted with an appropriately substituted lactone (*Tetrahedron*, **1984**, *40*, 1313) to give a hemiketal. The acetal is then cleaved with an acidic such as p-TsOH in a solvent such as water to give a hydroxyketone. The sulfide is then oxidized with a reagent such as Oxone®, in the presence of a phase transfer reagent such as Aliquat 336® in solvents such as t-BuOH and water to give a sulfone. The hydroxyketone is then esterified with an appropriately substituted acetic acid with reagents such as CMC and DMAP in a solvent such as CH_2Cl_2 to give an intermediate ester which is cyclized with a base such as DBU to give lactone **Im**.

T660X

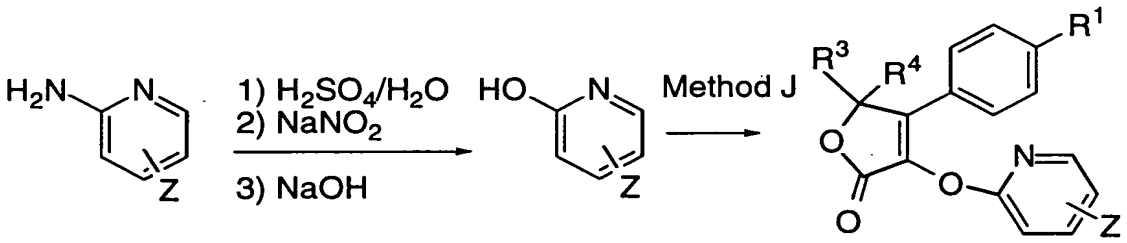


Ia R^1=SO_2Me

66

Method S

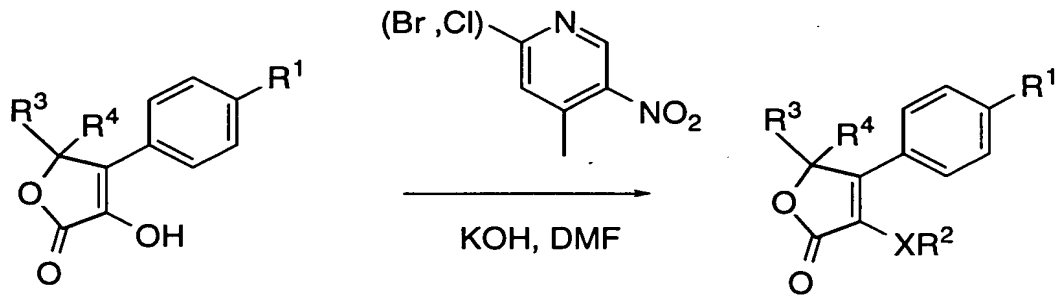
An appropriately substituted aminopyrydine is diazotized with $NaNO_2$ in an acid such as H_2SO_4 in water, followed by neutralization with NaOH affords an hydroxypyridine which is reacted following the method J.



Ii $R^1=SO_2Me$
Z=alkyl
X=O

Method T

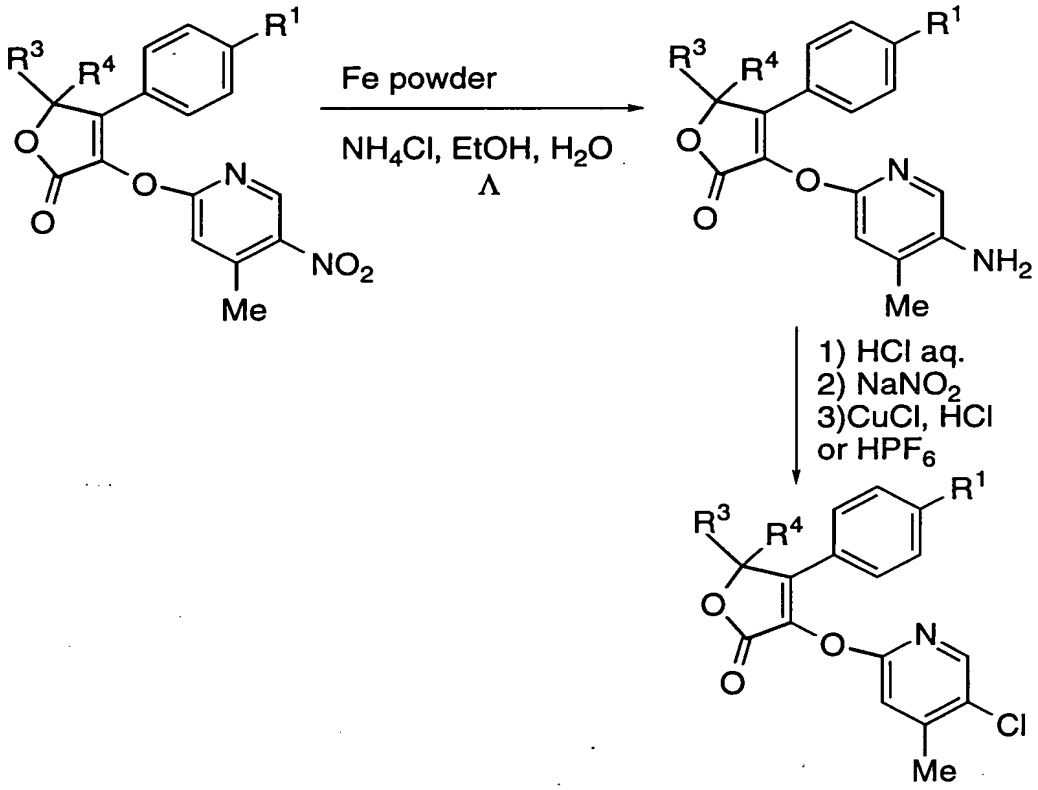
An appropriately substituted hydroxylactone is treated with a base such as KOH in a solvent such as DMF, followed by treatment with an appropriately substituted halopyridine afford lactone **Ii**.



Ii $R^1=SO_2Me$
R^2=pyridine
X=O

Method U

An appropriately substituted nitropyridine is reduced with a reagent such as Fe (powder) and NH_4Cl in solvents such as ethanol and water to give an aminopyridine which is diazotized with $NaNO_2$ in aqueous HCl, the diazonium salt is decomposed with copper salts such as CuCl in HCl to give lactone **Ii**.

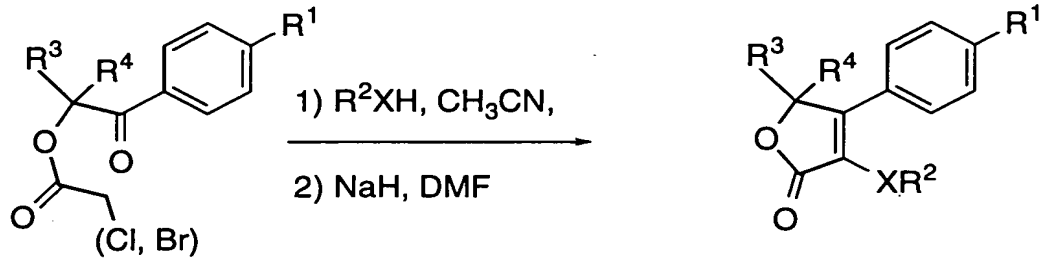


Ii R^1=SO_2Me
R^2=pyridine

Method W

An appropriately substituted halo acetate is reacted with an appropriate secondary amine ($R^2(R^{15})NH$) in a solvent such as CH_3CN; further treatment with a base such as NaH in a solvent such as DMF affords lactone **Ia**.

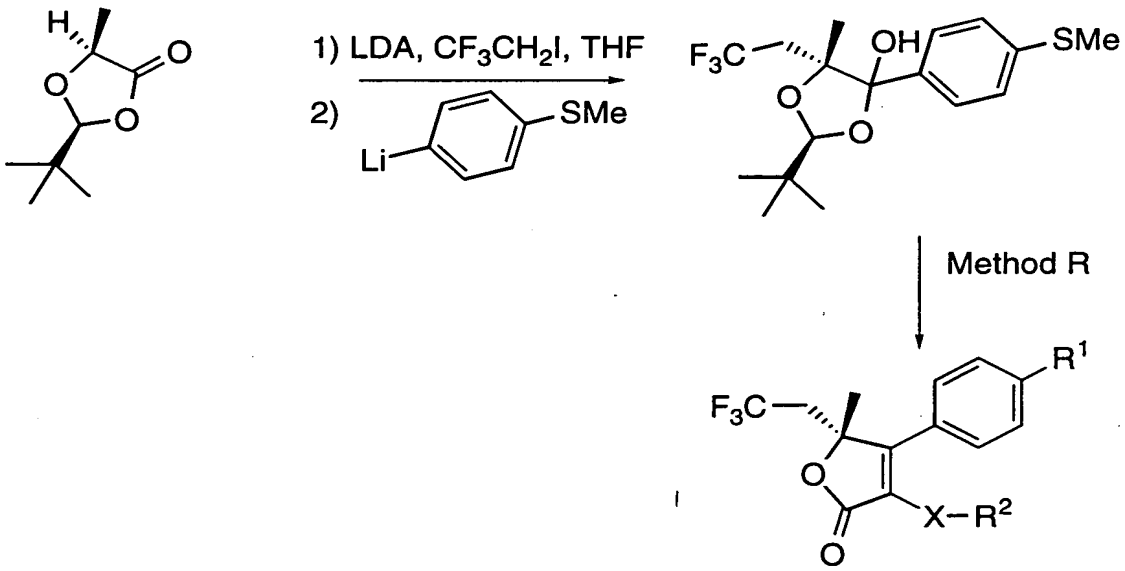
7690X



Ia $R^1=SO_2Me$
$X=N(R^{15})$

Method X

An appropriately substituted lactone (*Tetrahedron* , **1984**, *40*, 1313) is treated with a base such as LDA and reacted with 2,2,2-trifluoroiodoethane. Further treatment with the lithium salt of 4-bromothioanisole gives the desired hemiketal, which is then reacted as in method R to give the desired lactone **Im**.

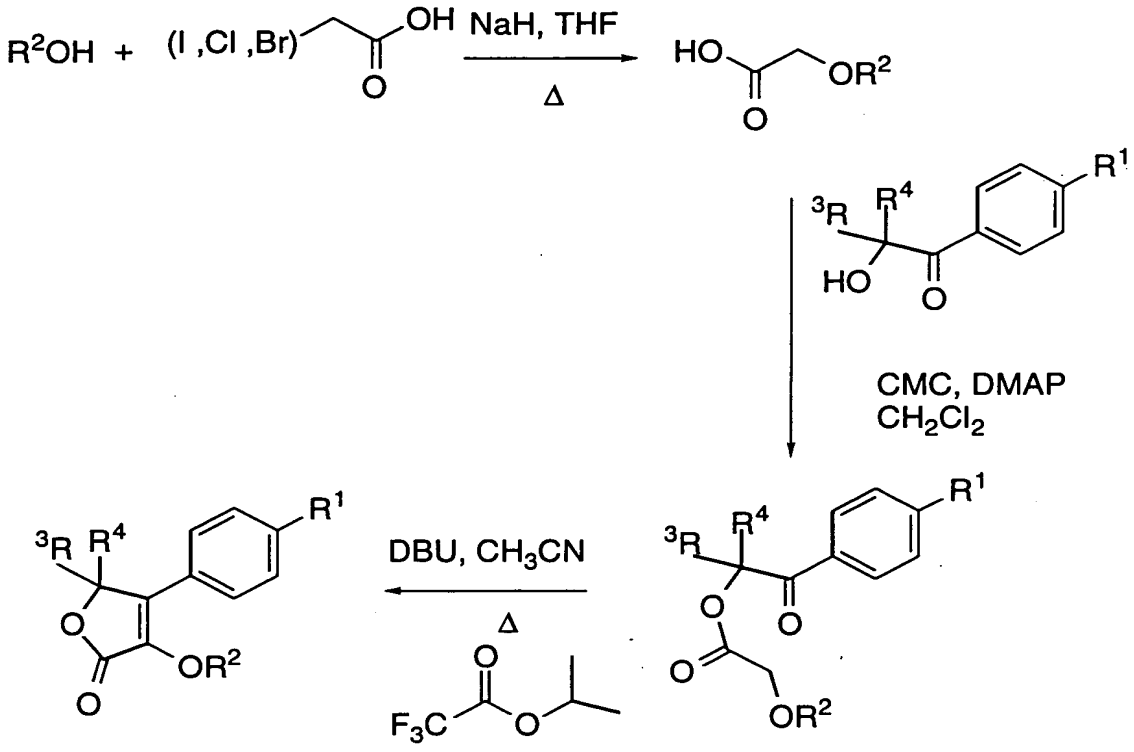


7691X

Im $R^1=SO_2Me$

Method Y

An appropriately substituted alcohol is reacted with an appropriate haloacid such as bromoacetic acid with a base such as NaH in a solvent such as THF to afford an acid ether which is then esterified with an appropriately substituted hydroxyketone with reagents such as CMC and DMAP in a solvent such as CH_2Cl_2 to give a ketoester. The ketoester is then cyclized in the presence of a base such as DBU and a dehydrating reagent such as iso-propyl trifluoroacetate in a solvent such as CH_3CN to afford lactone **Ia**.

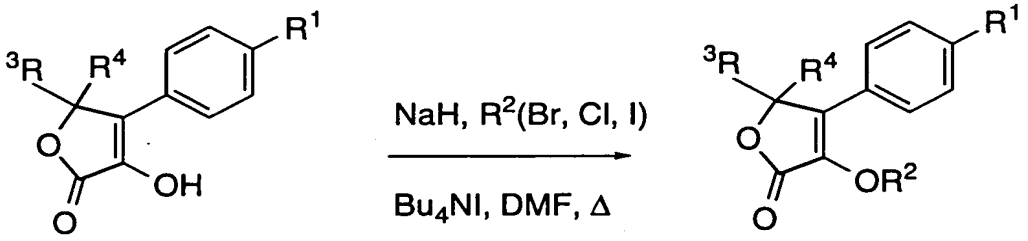


Ih $R^1=SO_2Me$

Method Z

An appropriately substituted hydroxylactone is reacted with an appropriate halide in the presence of a base such as NaH, with a reagent such as Bu4NI in a solvent such as DMF to afford lactone **Ih**.

T710X

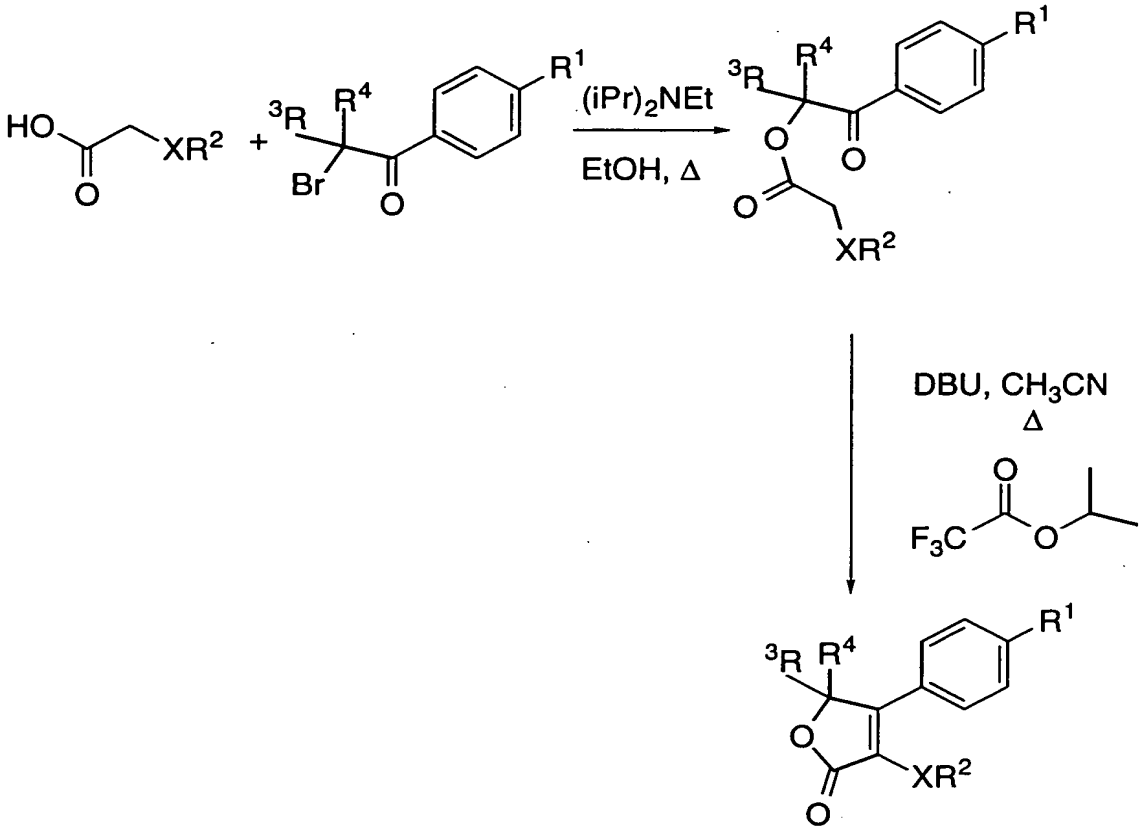


Ih $R^1=SO_2Me$

Method A-1

An appropriately substituted carboxylic acid is esterified with an appropriately substituted haloketone in the presence of a base such as $(iPr)_2NEt$ in a solvent such as EtOH; further treatment with a base such as DBU and a reagent such as iso-propyl 2,2,2-trifluoroacetate in a solvent such as CH_3CN affords lactone **Ia**.

T720X

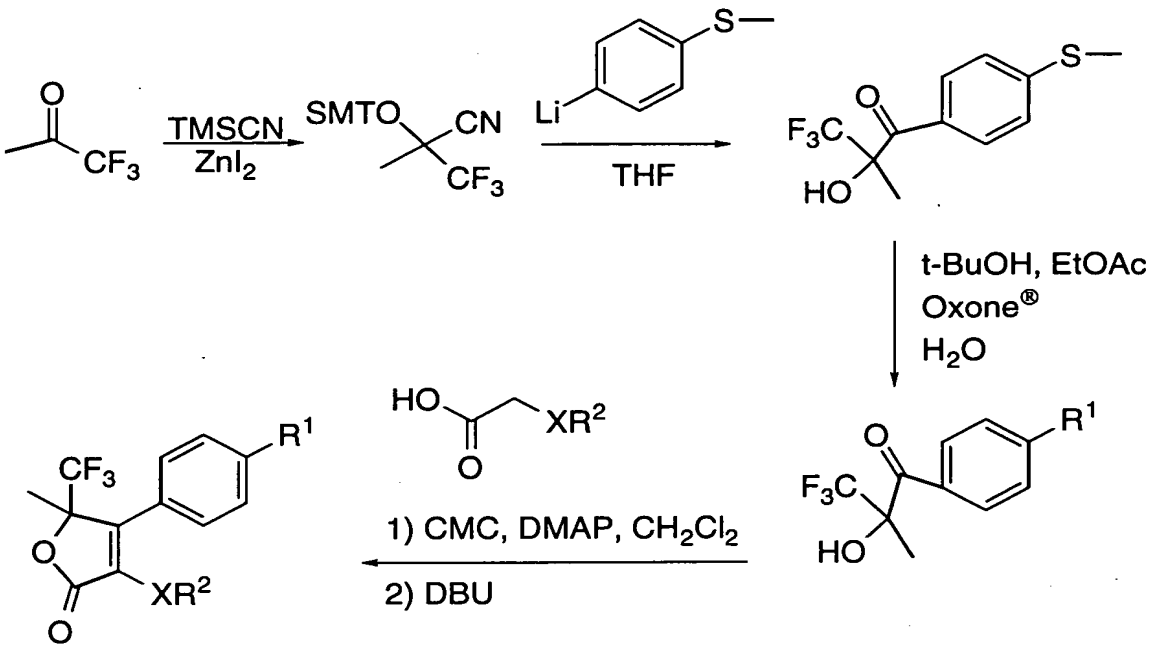


Ia $R^1=SO_2Me$

Method B-1

An appropriately substituted ketone is reacted with a reagent such as TMSCN in the presence of a Lewis acid such as ZnI_2, further treatment with a metal salt of thioanisole followed by hydrolysis affords an hydroxyketone. Oxidation of the sulfide with an oxidizing reagent such as Oxone® in solvents such as t-BuOH, EtOAc and water gives the sulfone. Esterification of the alcohol and an appropriately substituted acetic acid with a reagent such as CMC and DMAP in a solvent such as CH_2Cl_2 followed by treatment with a base such as DBU gives the lactone **In**.

T730X

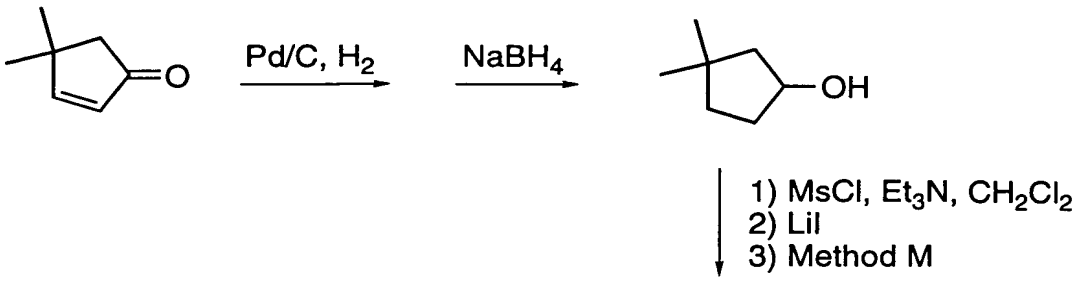


In $R^1=SO_2Me$

Method C-1

An appropriately substituted enone is reduced with hydrogen in a solvent such as ethyl acetate with a catalyst such as palladium on activated carbon to give an alcohol. This alcohol was transformed into a leaving group by treatment with reagents such as methanesulfonyl chloride and triethylamine in a solvent such as methylene chloride, followed by treatment in a solvent such as acetone with a reagent such as lithium iodide to afford a compound which was then reacted as in method M to afford lactone **Ij**.

T740X

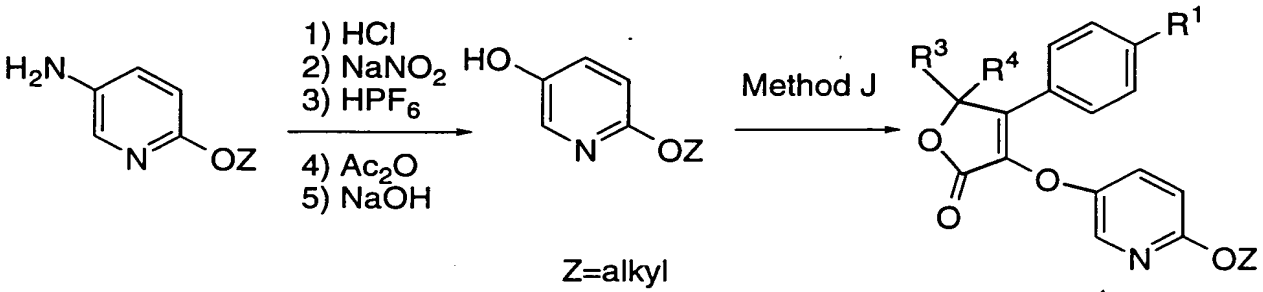


Ij $R^1=SO_2Me$

Method D-1

5-Amino-2-alkoxypyridine is converted to the corresponding diazonium salt and heated with acetic anhydride at 100-110°C. The corresponding 5-acetoxy-2-alkoxypyridine is then hydrolysed with sodium hydroxide to give the 5-hydroxy-2-alkoxypyridine which is reacted according to method J.

T741X



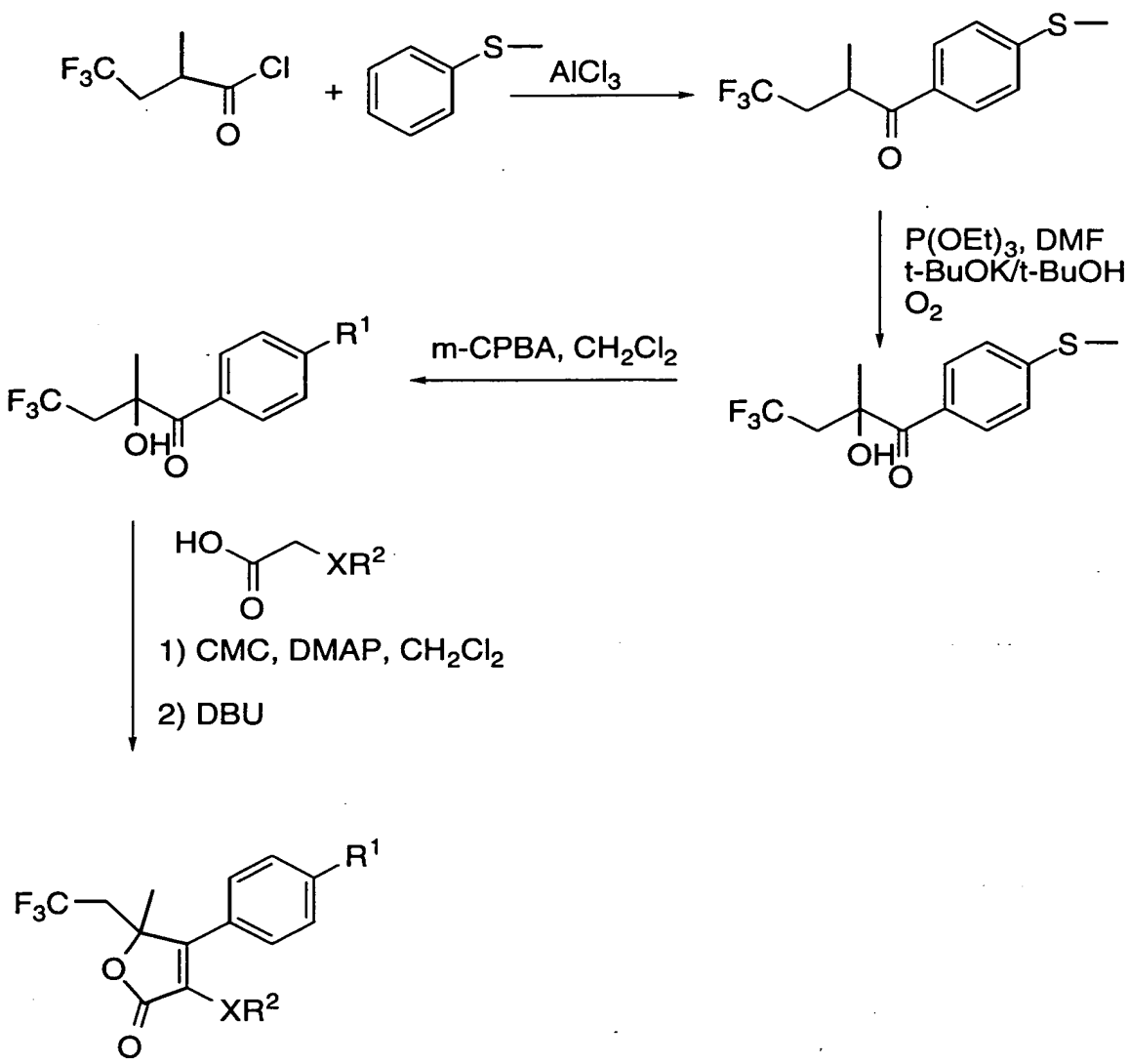
Ik $R^1= SO_2Me$
Z= alkyl

Method E-1

2(RS)-2-Methyl-4,4,4-trifluorobutyryl chloride(GB 2238790-A) is reacted with thioanisole in the presence of a Lewis acid such as $AlCl_3$. The ketone is then hydroxylated by air in the presence of potassium t-butoxide and triethyl phosphite, and the sulfide is then oxidized with m-CPBA to the sulfone. The hydroxyketone is then esterified with an appropriately substituted acid in the presence of CMC and DMAP in a solvent such as CH_2Cl_2 to give an intermediate ester which is cyclized with a base such as DBU to give lactone **Io**.

75

T760X

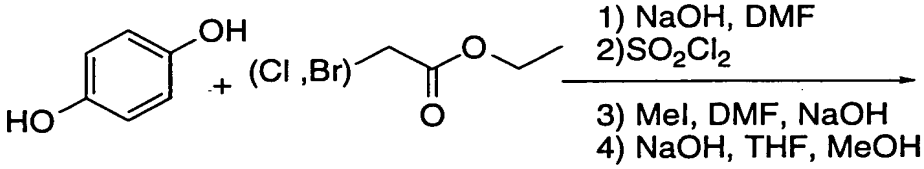


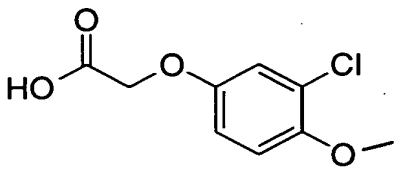
Io $R^1=SO_2Me$

76

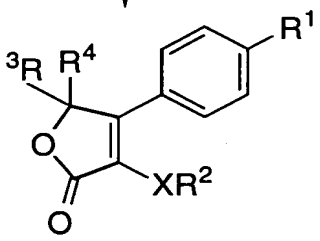
Method F-1

Hydroquinone is reacted with a halosubstituted acetate, chlorinated with sulfuryl chloride, methylated with iodomethane in the presence of a base and followed by hydrolysis with sodium hydroxide to give the substituted phenoxy acetic acid, which is reacted according to method A to afford lactone **Ia**.





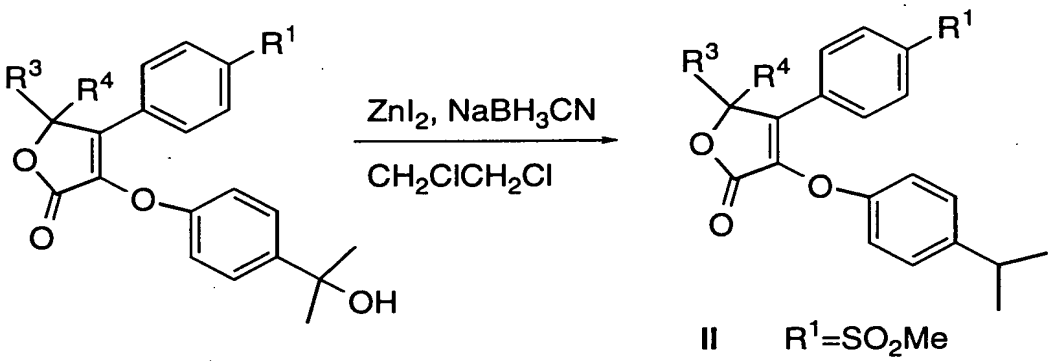
Method A



Ia $R^1=SO_2Me$

Method G-1

An appropriately substituted 3-(4-(1-hydroxy-1-methyl)ethylphenoxy)-5H-furan-2-one is reduced with $NaBH_3CN$ in the presence of ZnI_2 to give lactone **II.**

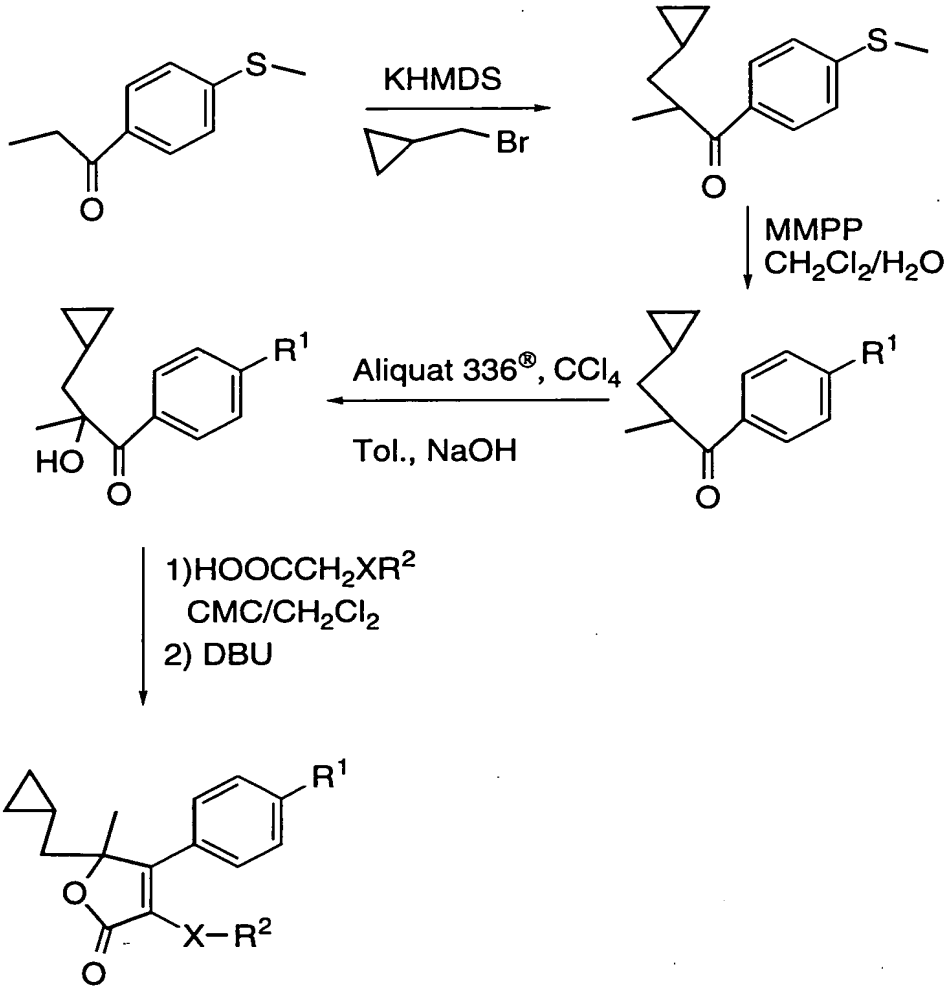


II $R^1=SO_2Me$

Method H-1

An appropriately substituted alkyl (4-thiomethyl)phenyl ketone is alkylated with bromomethylcyclopropane using a base such as KHMDS. The methyl sulfide is oxidized with MMPP to the corresponding sulfone and hydroxylated by NaOH and CCl_4 in toluene in the presence of a phase transfer catalyst such as Aliquat 336®. The hydroxyketone is then esterified with an appropriately substituted acid in the presence of CMC and DMAP in a solvent such as CH_2Cl_2 to give an intermediate ester which is cyclized with a base such as DBU to give lactone **Ip**.

T790X



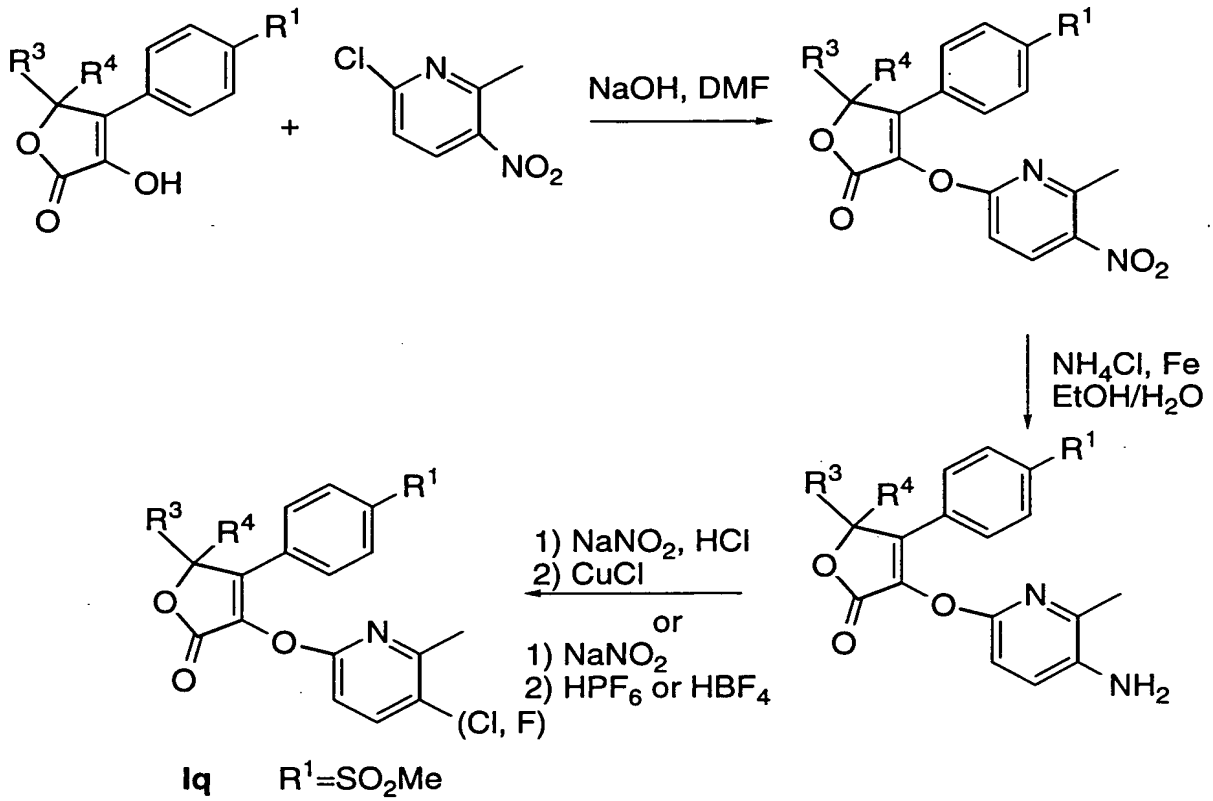
Ip $R^1=SO_2Me$

Method I-1

An appropriately substituted hydroxylactone is reacted with an appropriately substituted nitropyridine in the presence of a base such as NaOH in DMF at 100-110°C. The nitro group of the coupling product is then reduced with Fe (powder) and NH_4Cl in solvents such as ethanol and water. The amino group is diazotized and the resulting diazonium salt is decomposed in the presence of appropiate copper salt such as CuCl or CuBr to give lactone **1q**. Alternatively, the diazonium salt is treated

HBF_4 or HPF_6 to give after heating the fluoro-substituted lactone pyridine **Iq**.

T800X



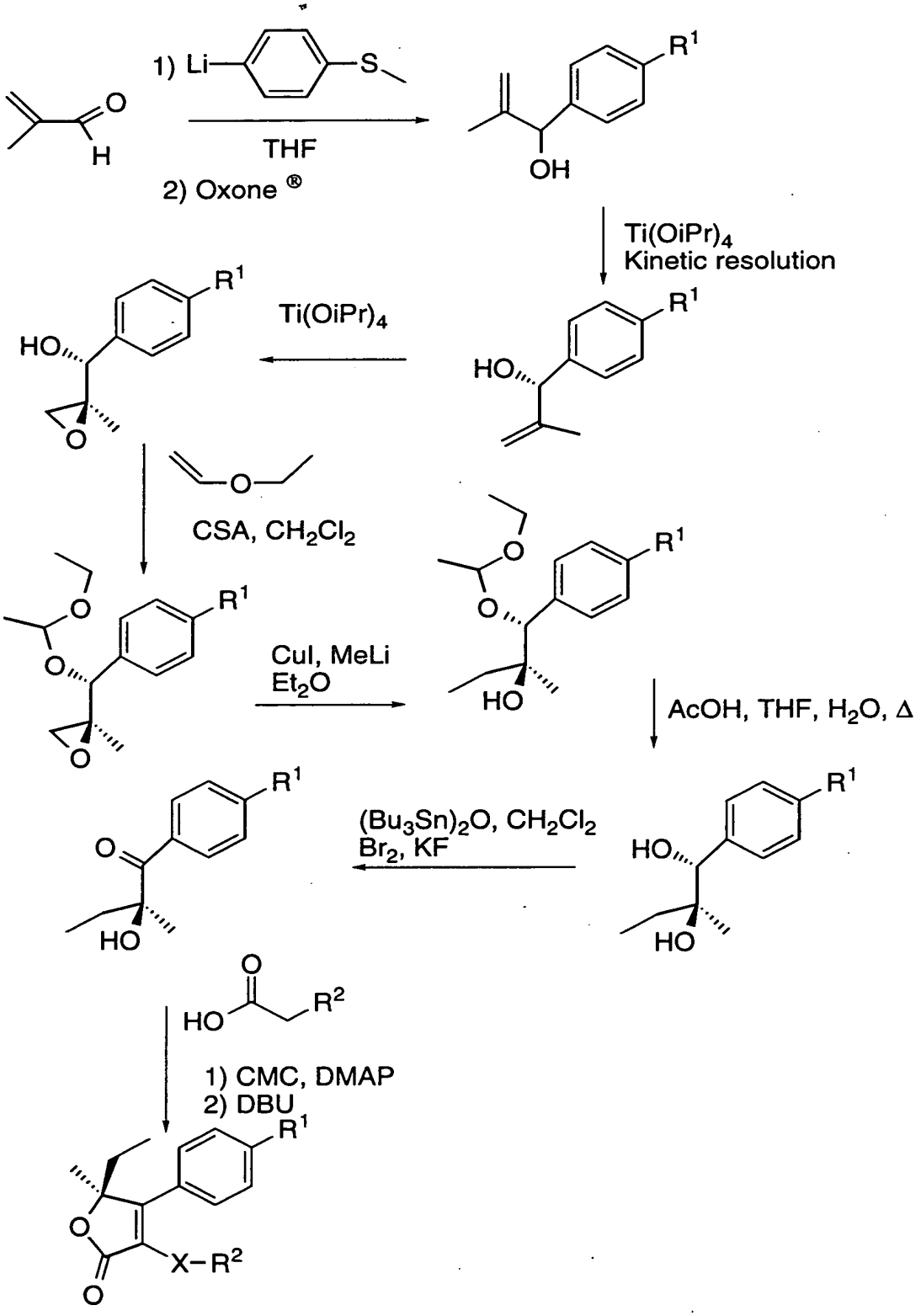
Iq $R^1=SO_2Me$

Method J-1

The lithium reagent prepared from 4-bromothioanisole and n-BuLi at -72°C is reacted with methacrolein and the resulting product is oxidized with an oxidizing reagent such as Oxone® to the methyl sulfone. A kinetic resolution by Sharpless epoxidation reaction using (+)-diisopropyl tartrate and t-butyl hydroperoxide provides the (S)-allylic alcohol, which is epoxidized by (-)-diisopropyl tartrate and t-butyl hydroperoxide. The alcohol of the epoxy alcohol is protected as an ethoxyethyl ether and the epoxide is reacted with dimethyl cuprate(from methyllithium and copper(I) iodide. The ethoxyethyl ether is then cleaved and the resulting diol is treated with $(Bu_3Sn)_2O$ and oxidized with Br_2 to give the (S)-alcohol. The hydroxyketone is then esterified with an appropriately substituted acid in the presence of CMC and DMAP in a

solvent such as CH_2Cl_2 to give an intermediate ester which is cyclized with a base such as DBU to give lactone **Ir**.

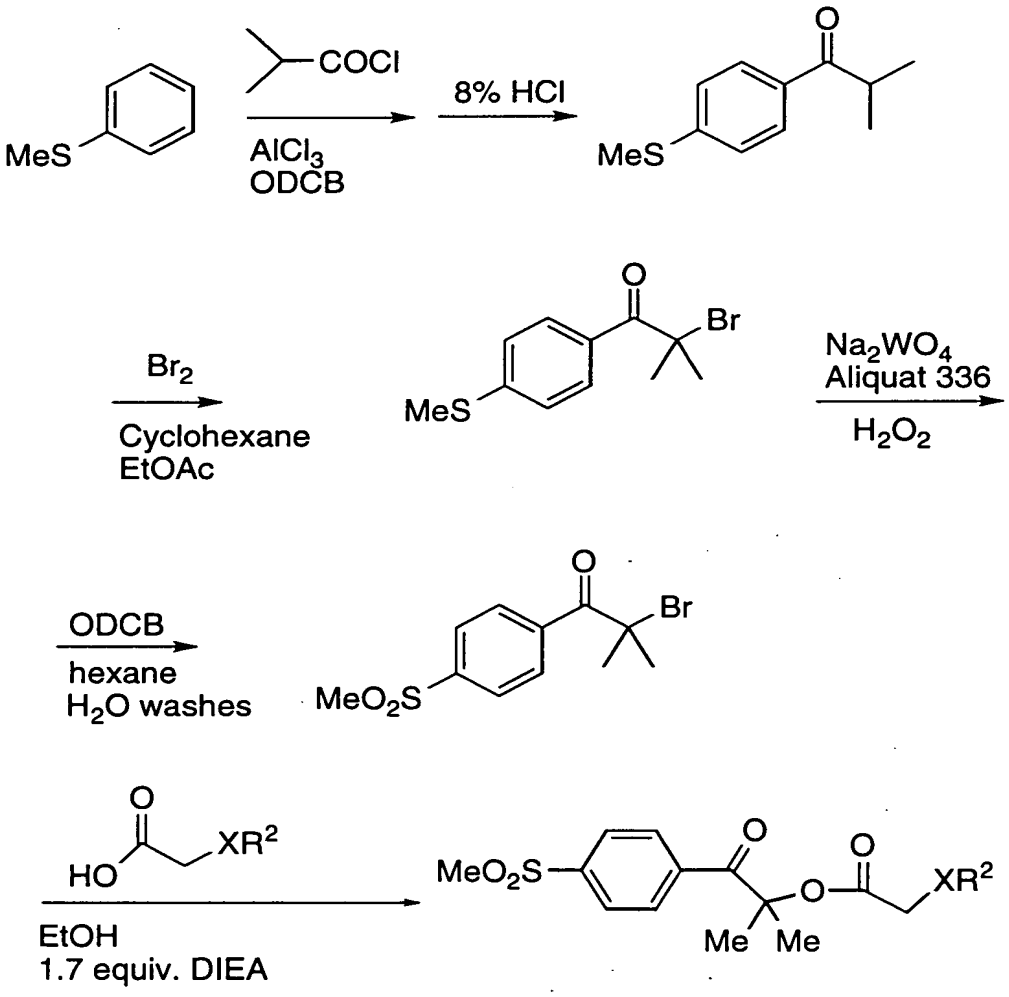
T820X



Ir R^1=SO_2Me

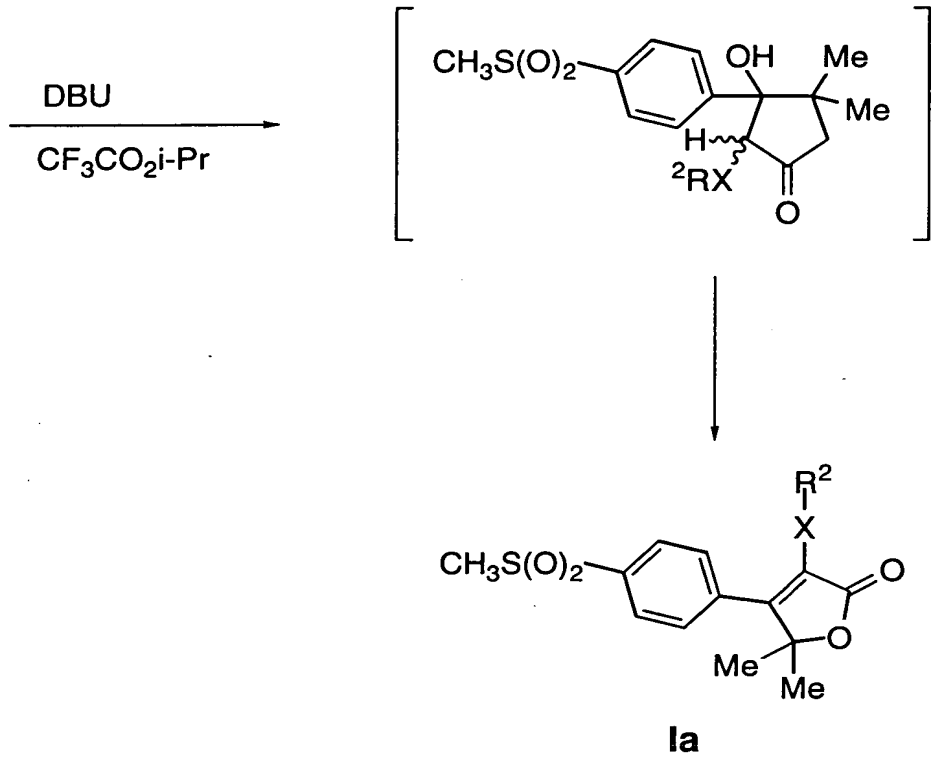
Method K-1

4-Bromothioanisole is reacted with isobutyryl chloride in the presence of aluminum chloride in o-dichlorobenzene(ODCB). The resulting ketone is brominated and oxidized with Na_2WO_4 and H_2O_2 in the presence of Aliquat 336 to the bromoketone methyl sulfone. The bromoketone is then reacted with an appropriate alkoxy or aryloxy acetic acid in the presence DIEA and the ester intermediate is cyclized and dehydrated with DBU in the presence of isopropyl trifluoroacetate to give lactone **1a**.



T830X

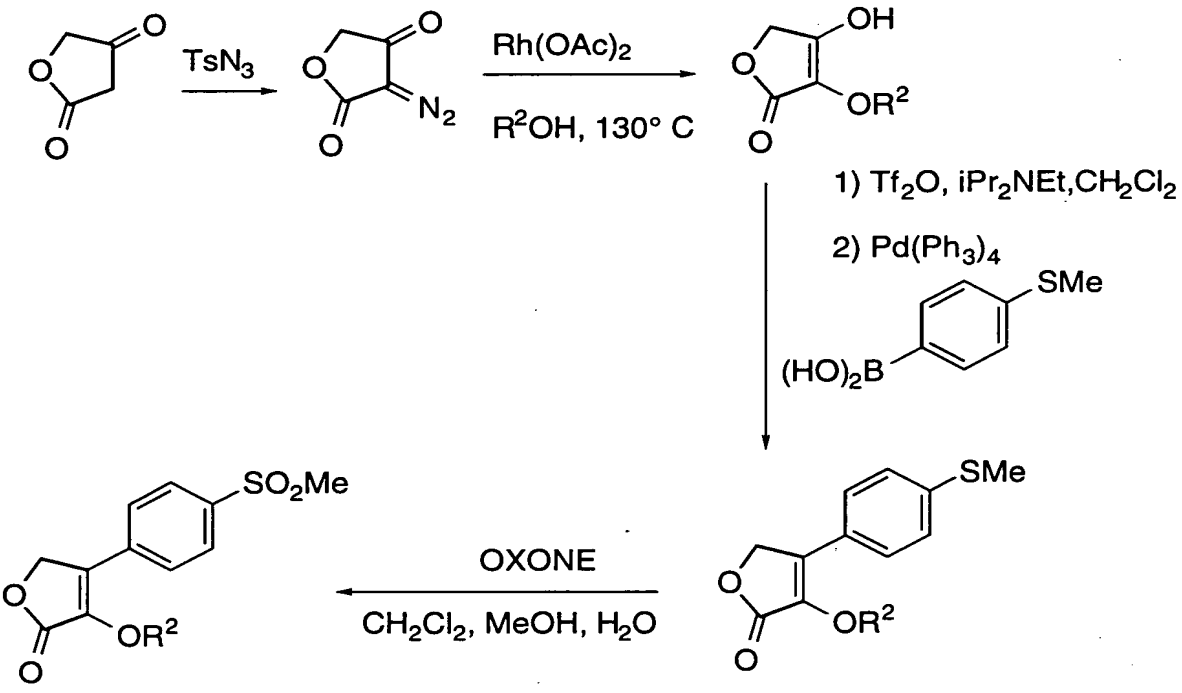
93



Ia

METHOD L-1

Tetronic acid is converted to the α-diazoketone derivative with tosyl azide (see Stachel et al., Liebigs Ann. Chem. 1994, P.129 for a similar preparation). The diazo compound is reacted with an appropriately substituted alcohol in the presence of rhodium acetate (see Stachel et al., Liebigs Ann. Chem. 1994 P. 129) to give an ether. This compound is treated with triflic anhydride followed by a Suzuki type coupling reaction with 4-methylthiophenyl boronic acid (Wong et al., Tetrahedron Lett. 1993, p. 8237.) The sulfide is then oxidized with OXONE® to provide Is.



Is

T850X

Representative Compounds

Tables I illustrates novel compounds of the present invention.

Table I

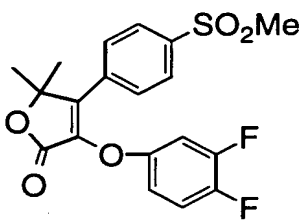
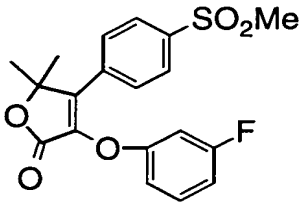
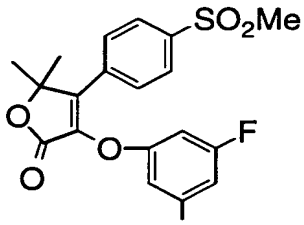
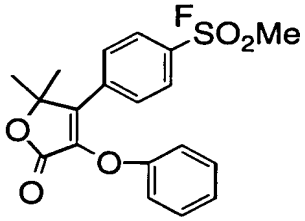
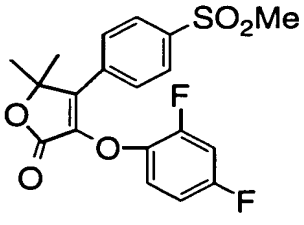
	Example	Method
	1	A
	2	A
	3	A
	4	F
	5	B

Table I (continued)

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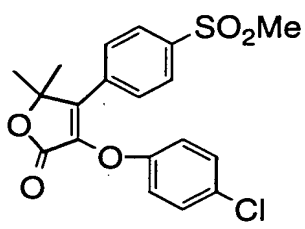
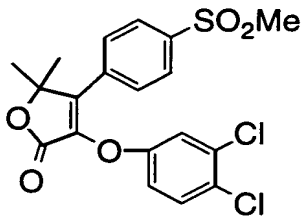
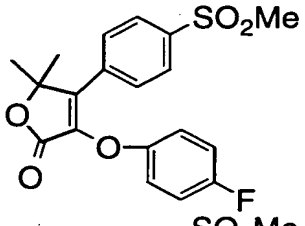
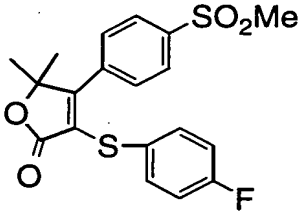
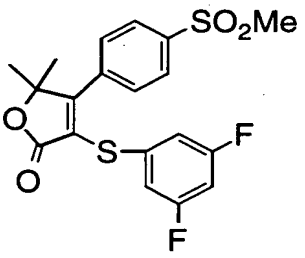
	6	A
	7	A
	8	A
	9	A
	10	C

Table I (continued)

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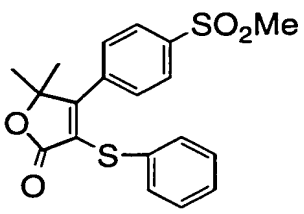
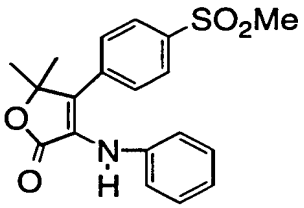
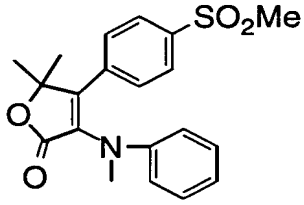
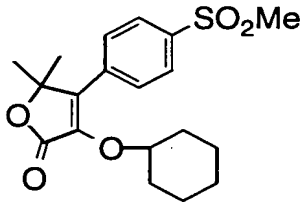
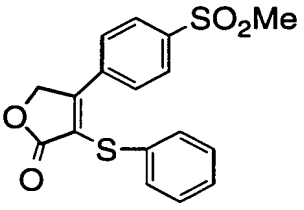
	11	A
	12	D
	13	D
	14	E
	15	E

Table I (continued)

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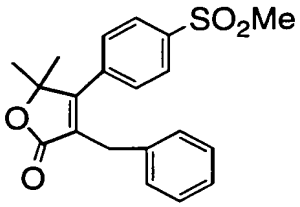
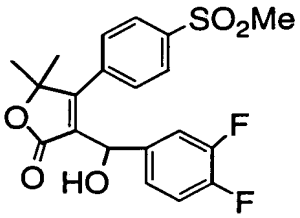
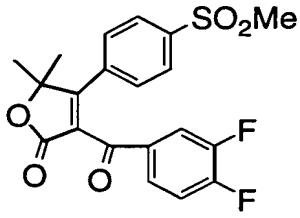
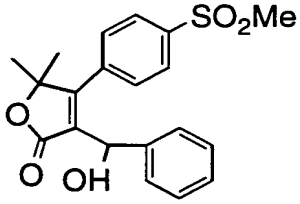
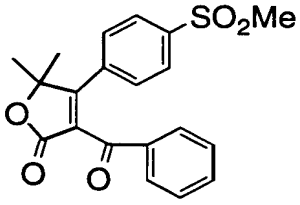
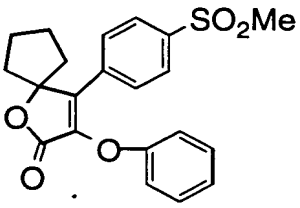
	16	F
	17	G
	18	G
	19a	G
	19b	G
	20	A

Table I (continued)

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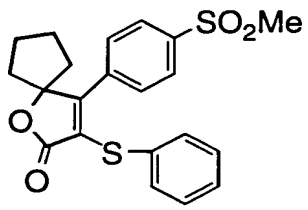
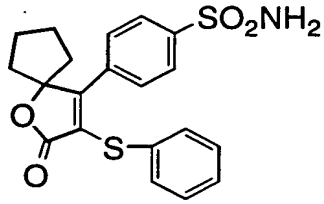
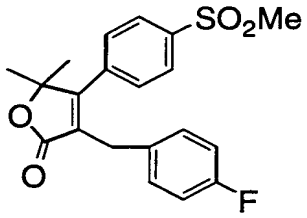
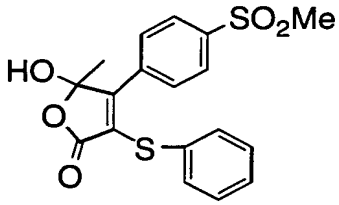
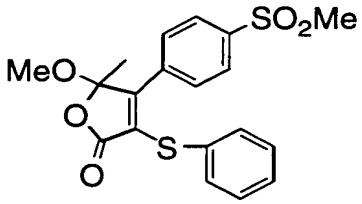
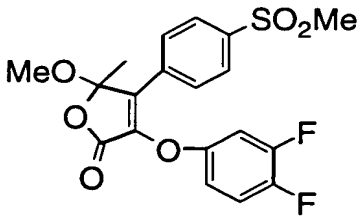
	21	A
	22	H
	23	F
	24a	I
	24b	I
	24c	I

Table I (continued)

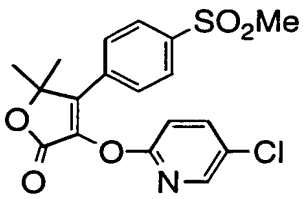
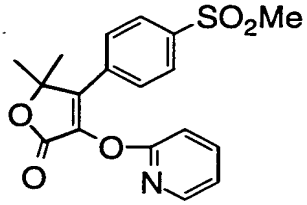
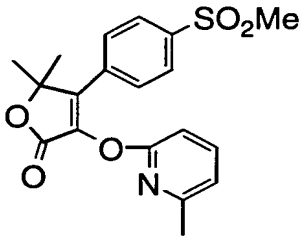
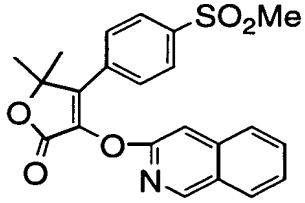
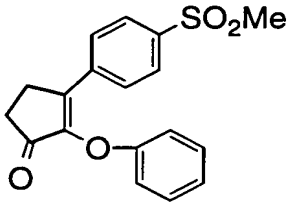
Example	Method
	25 J
	26 J
	27 J
	28 J
	29 K

Table I (continued)

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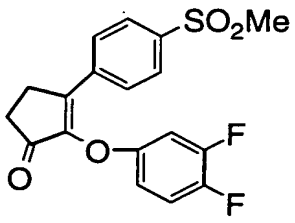
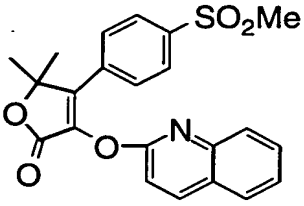
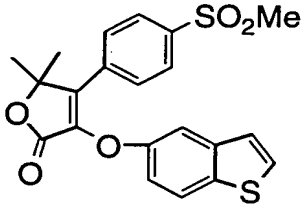
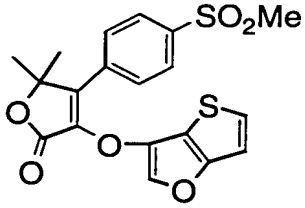
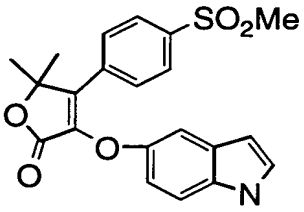
	30	Q
	31	J
	32	J
	33	
	34	

Table I (continued)

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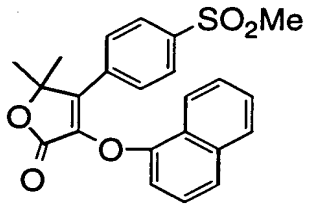
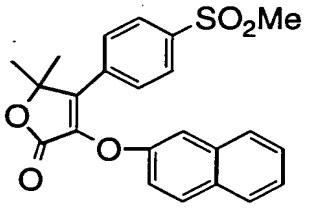
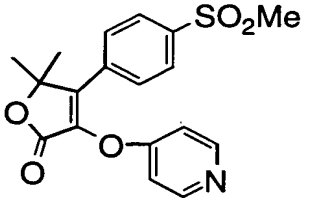
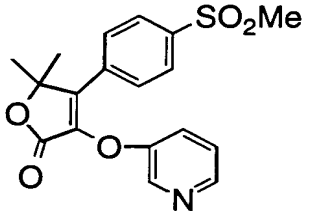
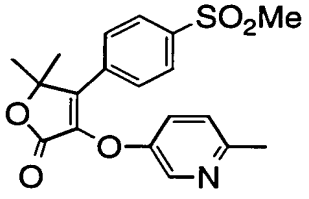
	35	
	36	
	37	J
	38	J
	39	J

Table I (continued)

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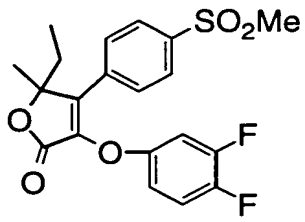
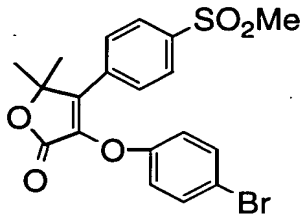
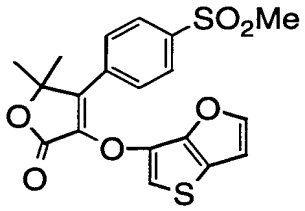
	40	
	41	
	42	

Table I (continued)

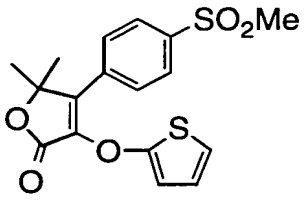
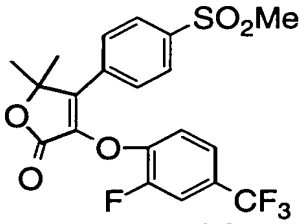
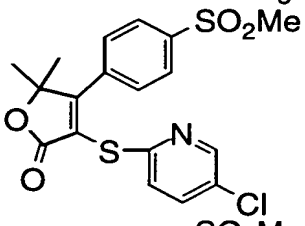
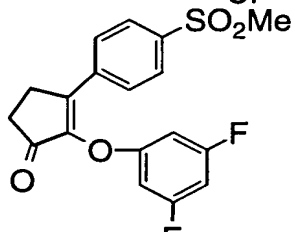
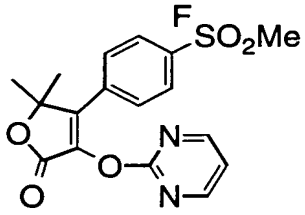
Example	Method
	43	
	44	J
	45	J
	46	K
	47	J

Table I (continued)

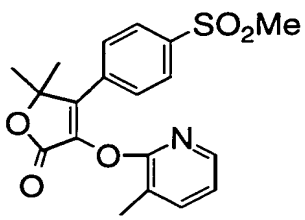
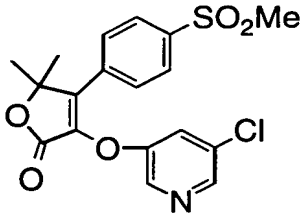
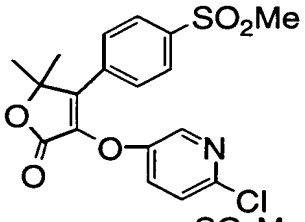
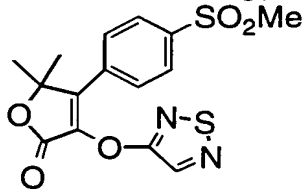
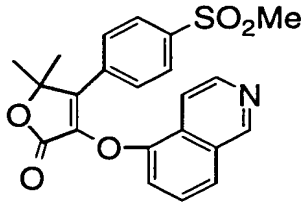
	Example	Method
	48	S
	49	J
	50	J
	51	J
	52	J

Table I (continued)

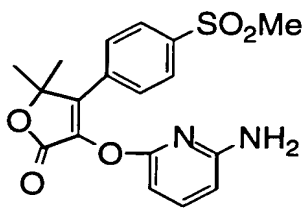
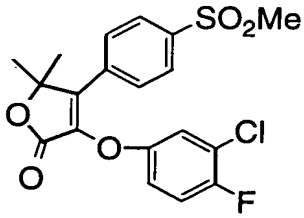
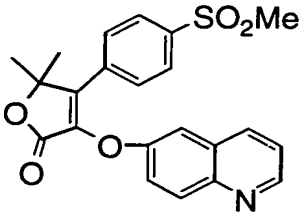
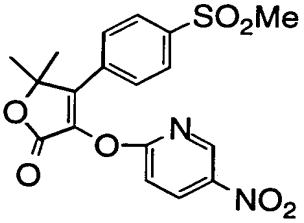
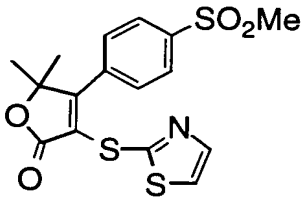
	Example	Method
	53	J
	54	J
	55	J
	56	J
	57	J

Table I (continued)

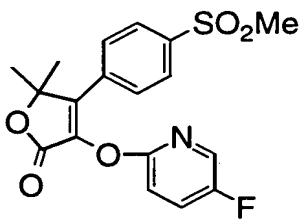
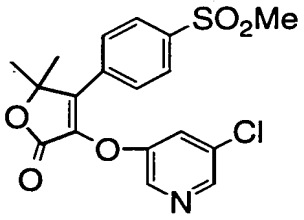
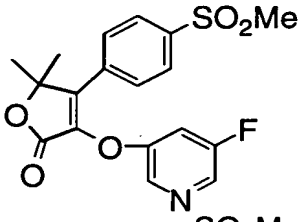
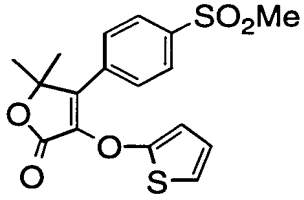
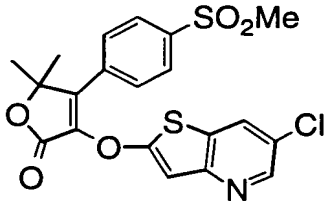
Example	Method
	58	J
	59	
	60	
	61	
	62	

Table I (continued)

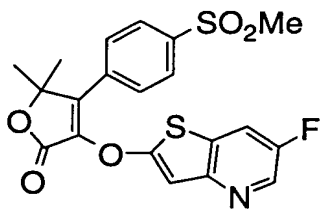
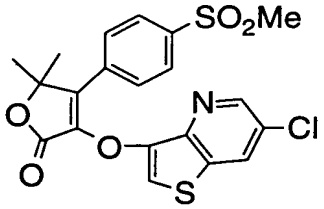
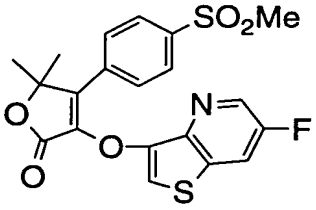
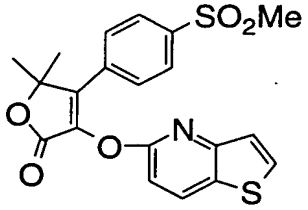
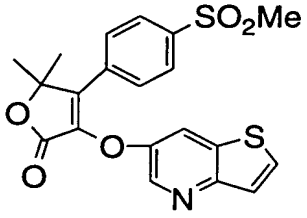
Example	Method
	63
	64
	65
	66
	67

Table I (continued)

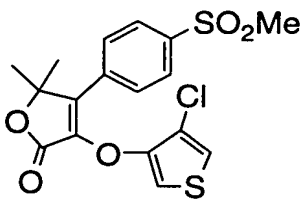
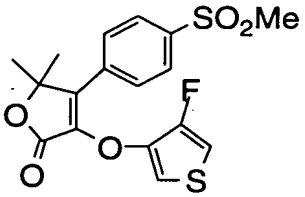
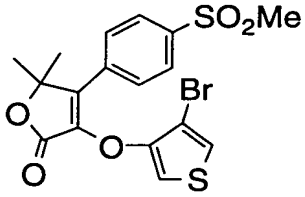
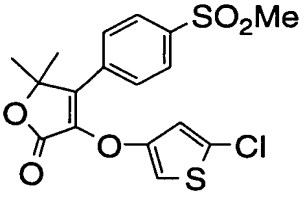
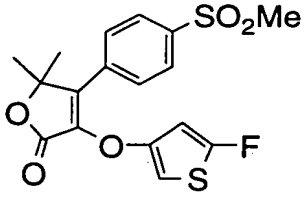
Example	Method
	68
	69
	70
	71
	72

Table I (continued)

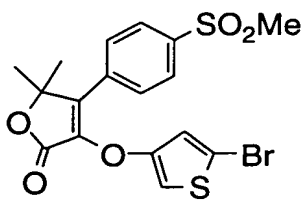
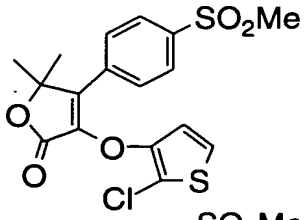
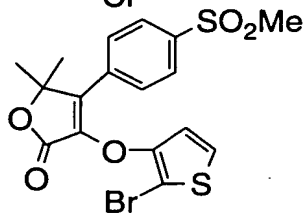
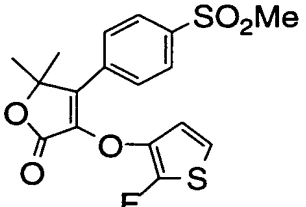
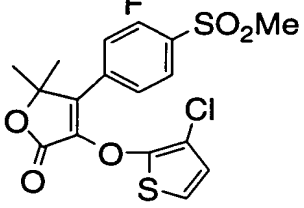
Example	Method
	73
	74
	75
	76
	77

Table I (continued)

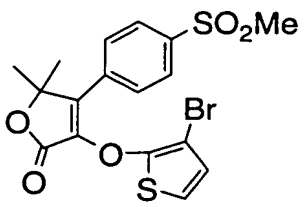
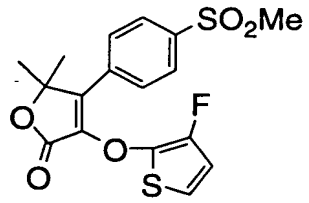
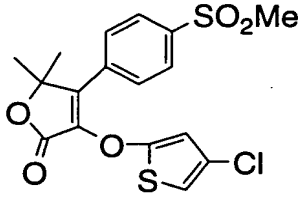
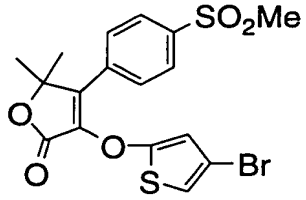
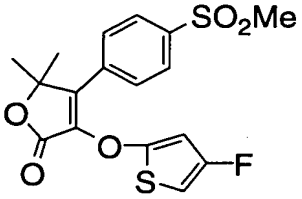
Example	Method
	78
	79
	80
	81
	82

Table I (continued)

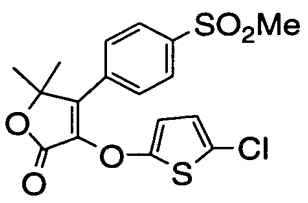
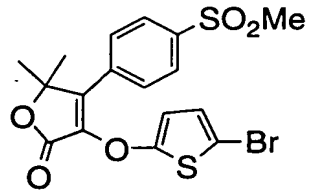
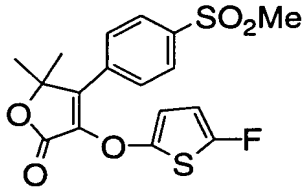
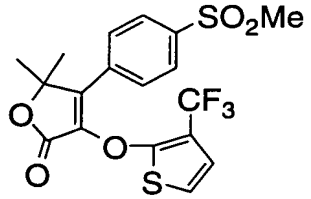
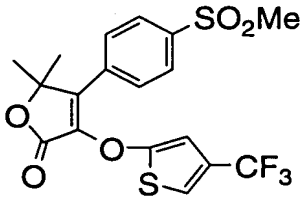
Example	Method
	83
	84
	85
	86
	87

Table I (continued)

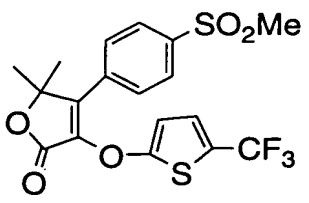
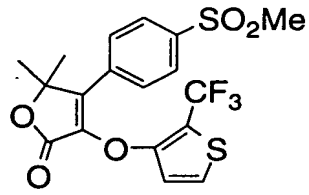
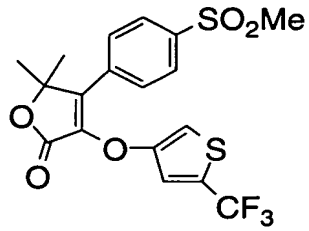
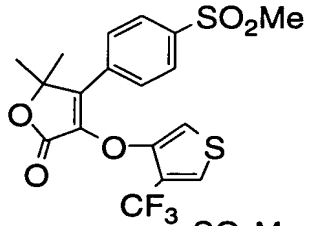
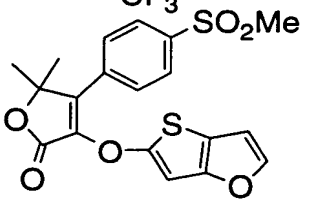
Example	Method
	88
	89
	90
	91
	92

Table I (continued)

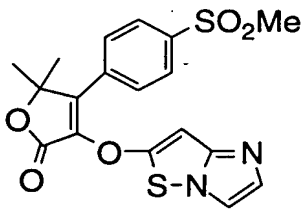
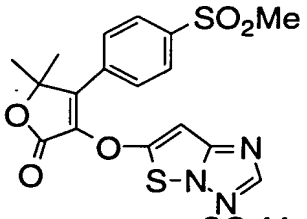
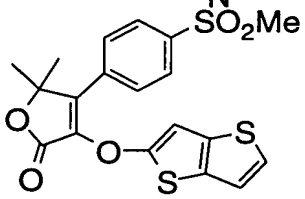
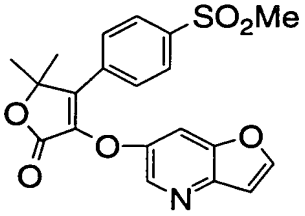
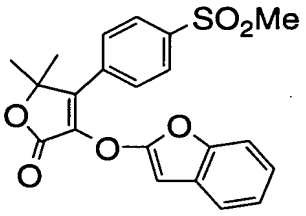
Example	Method
	93
	94
	95
	96
	97

Table I (continued)

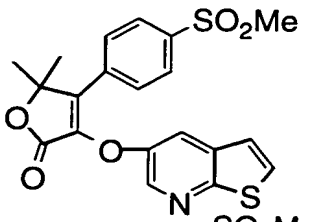
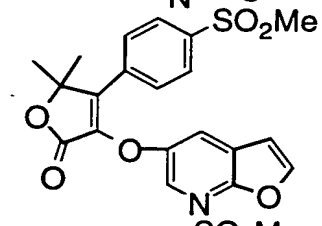
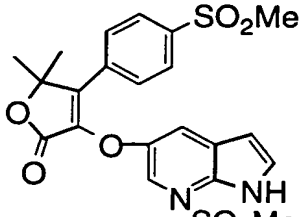
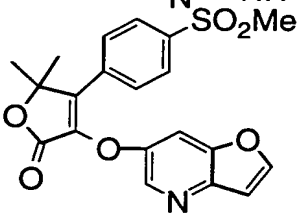
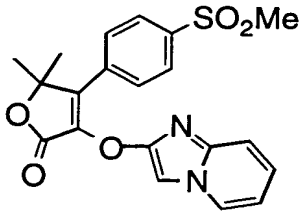
Example	Method
	98
	99
	100
	101
	102

Table I (continued)

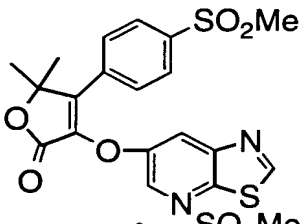
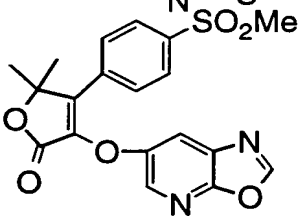
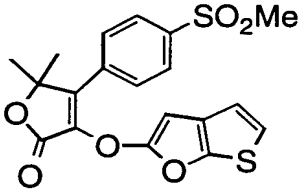
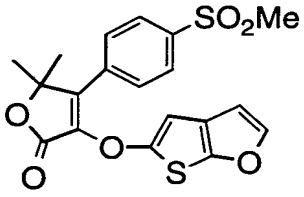
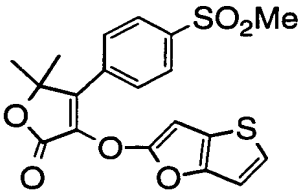
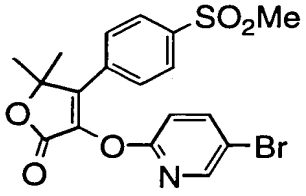
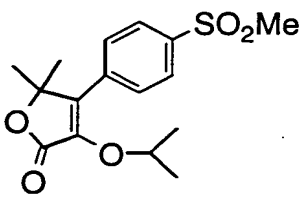
	Example	Method
	103	
	104	
	105	
	106	
	107	
	108	L
	109	M or K-1

Table I (continued)

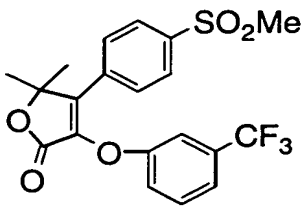
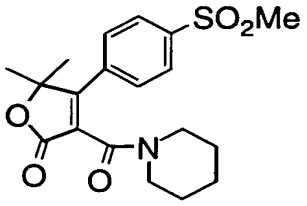
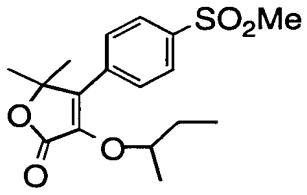
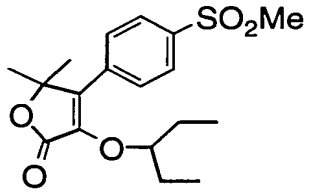
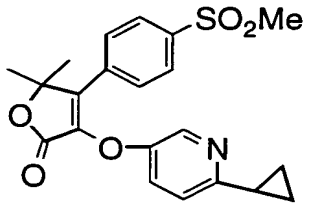
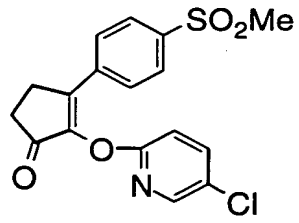
	Example	Method
	110	J
	111	N
	112	M
	113	O
	114	
	115	K

Table I (continued)

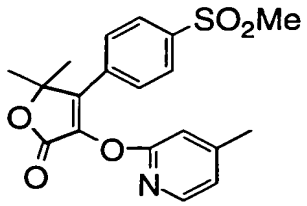
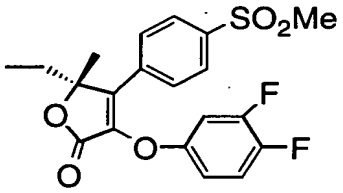
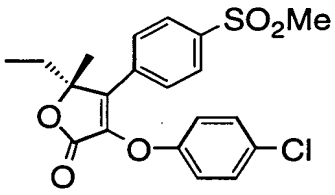
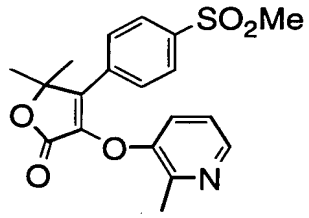
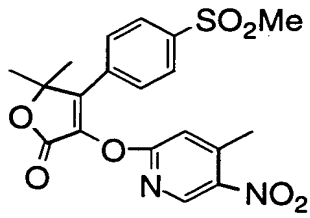
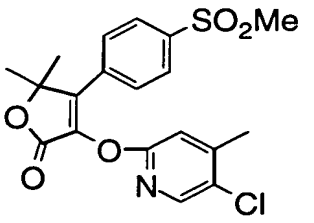
	Example	Method
	116	J
	117	R
	118	R
	119	J
	120	T
	121	U

Table I (continued)

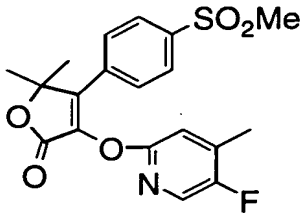
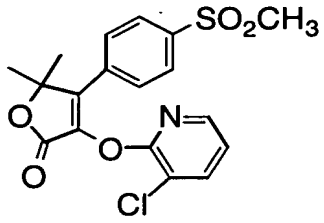
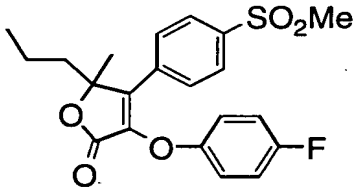
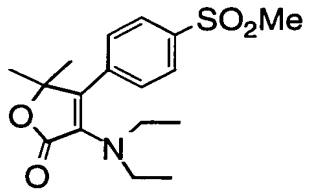
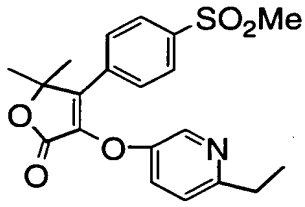
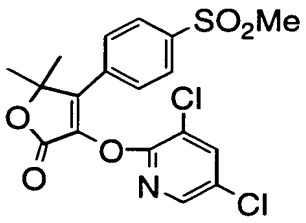
	Example	Method
	122	U
	123	T+U
	124	J
	125	W
	126	
	127	J

Table I (continued)

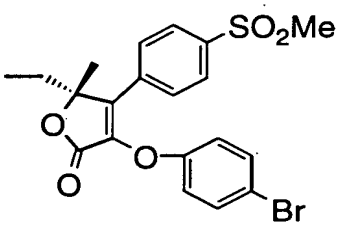
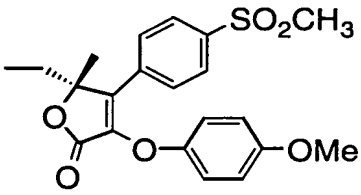
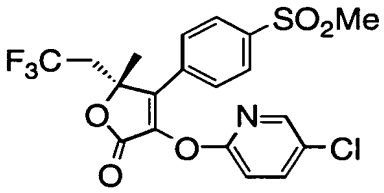
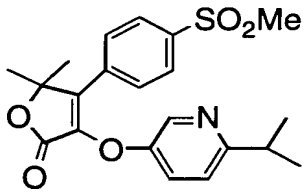
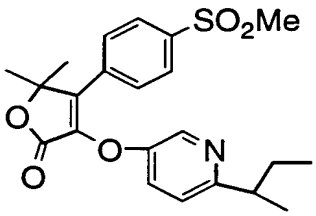
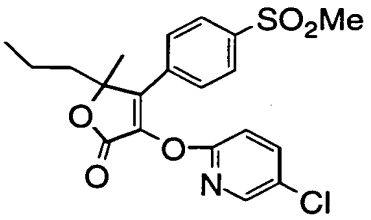
	Example	Method
	128	R
	129	J
	130	X+R
	131	
	132	
	133	J

Table I (continued)

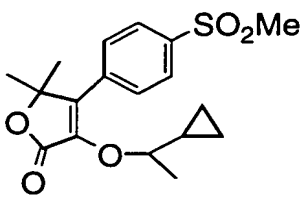
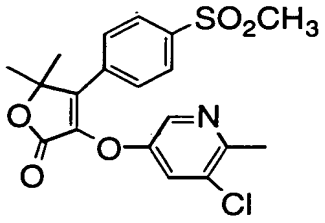
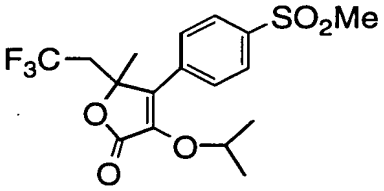
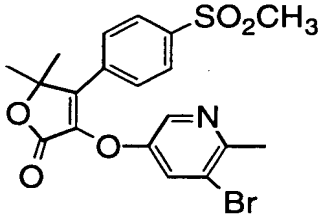
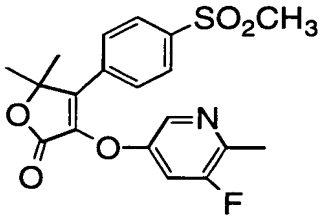
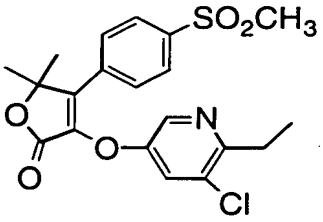
	Example	Method
	134	Y
	135	
	136	M
	137	
	138	
	139	

Table I (continued)

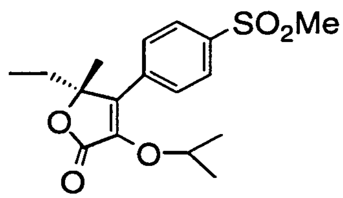
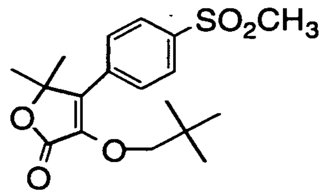
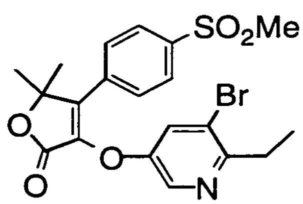
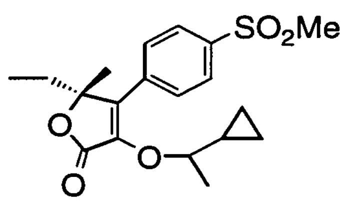
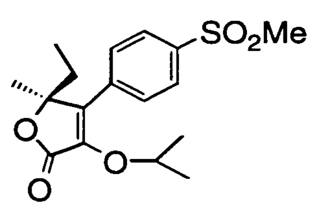
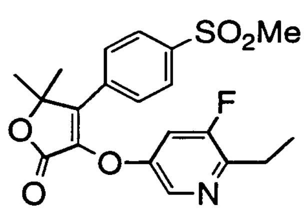
	Example	Method
	140	M
	141	Z
	142	
	143	Y
	144	J-1
	145	

Table I (continued)

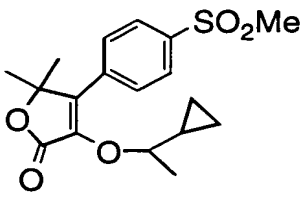
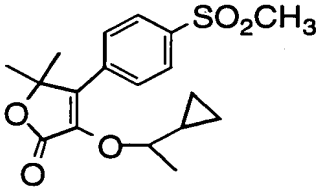
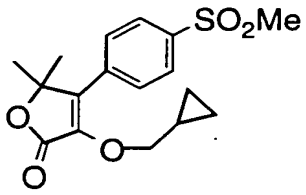
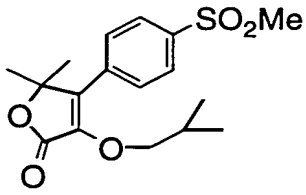
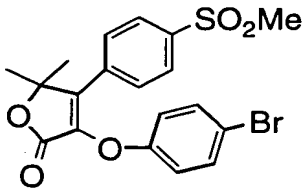
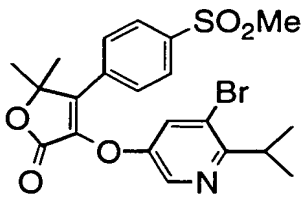
	Example	Method
	146	Y
	147	Y
	148	Z
	149	Z
	150	A
	151	

Table I (continued)

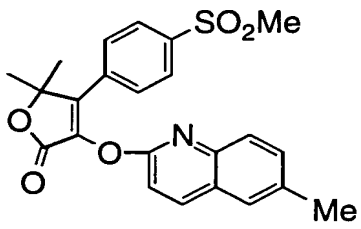
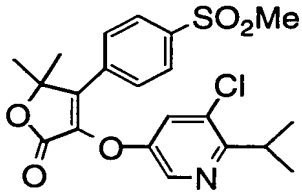
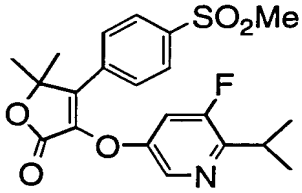
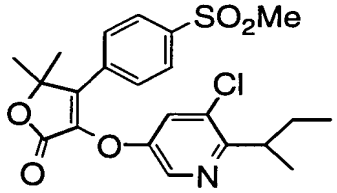
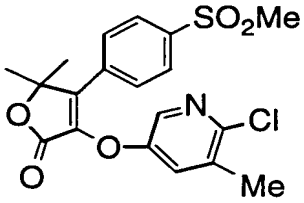
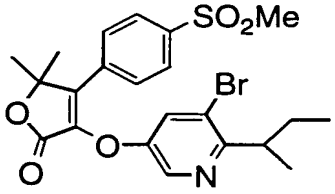
	Example	Method
	152	
	153	
	154	
	155	
	156	
	157	

Table I (continued)

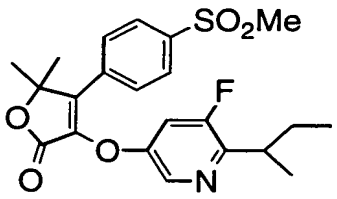
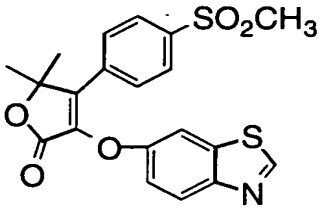
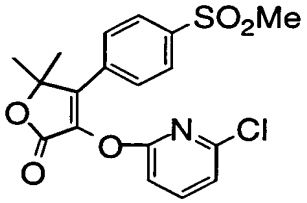
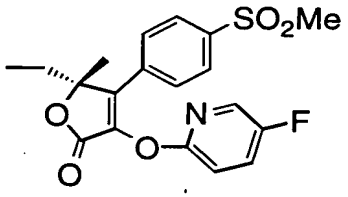
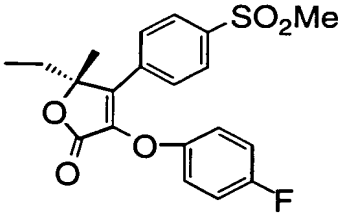
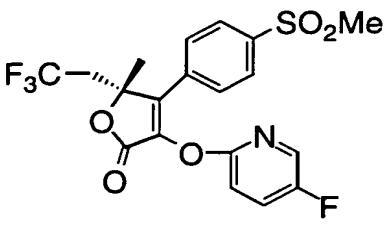
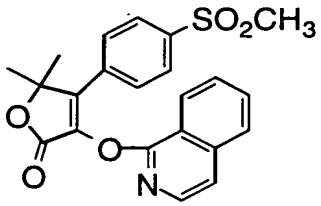
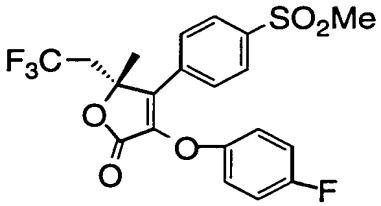
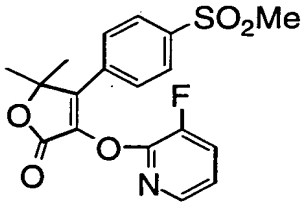
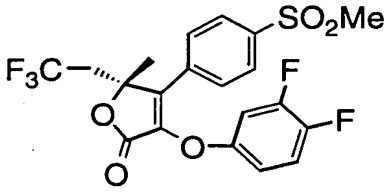
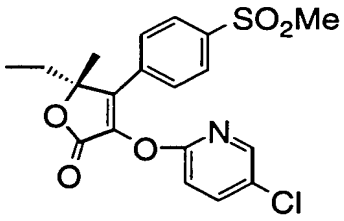
	Example	Method
	158	
	159	J
	160	J
	161	J
	162	J
	163	A

Table I (continued)

	Example	Method
	164	J
	165	J
	166	A
	167	B
	168	X+J
	169	A

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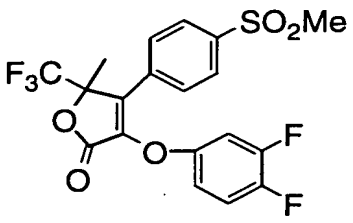
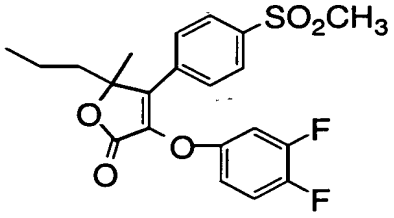
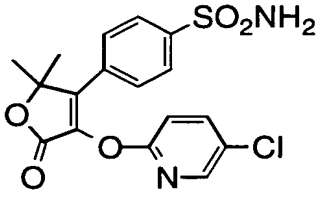
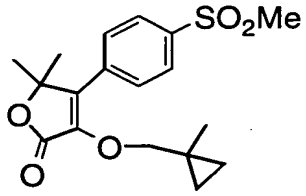
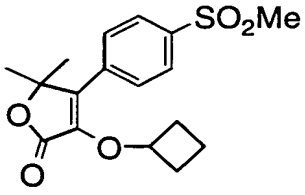
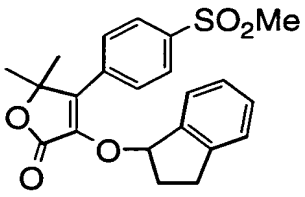
	170	B-1
	171	A
	172	
	173	
	174	E
	175	E

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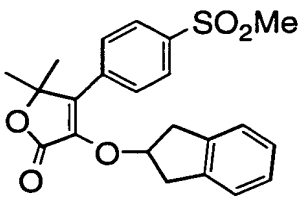
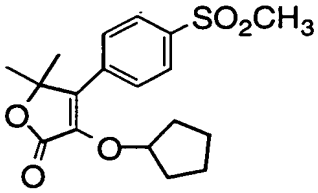
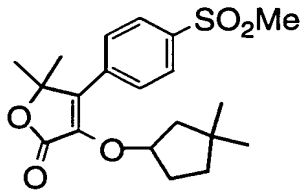
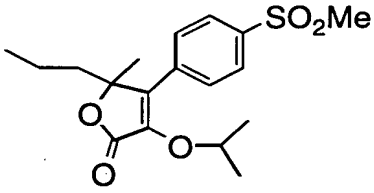
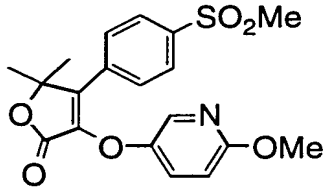
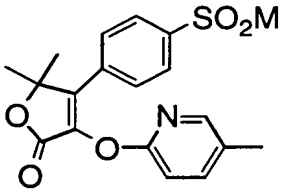
	176	E
	177	M
	178	C-1
	179	A
	180	D-1
	181	J

Table I (continued)

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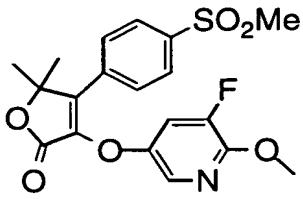
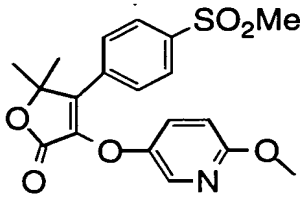
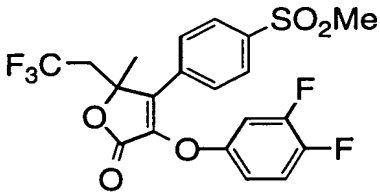
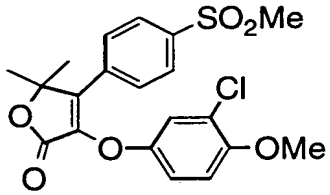
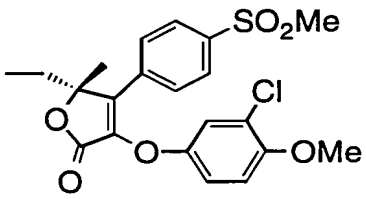
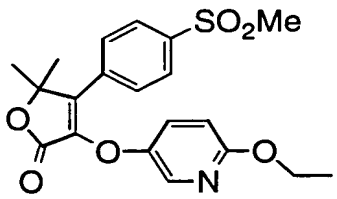
	182	
	183	
	184	E-1
	185	F-1+A
	186	F-1+A
	187	

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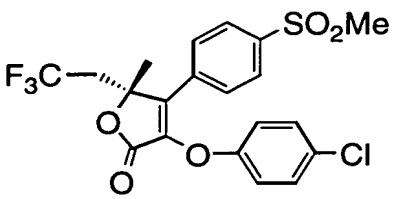
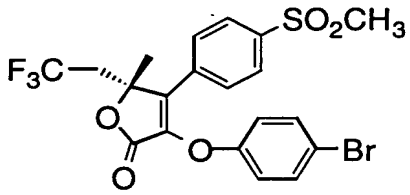
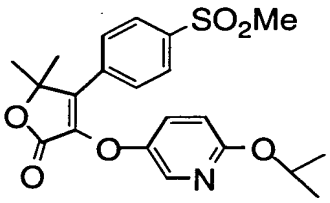
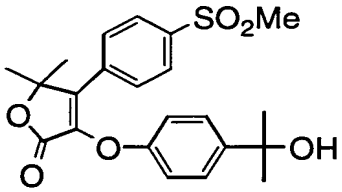
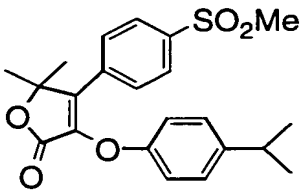
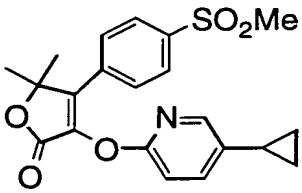
	188	R
	189	R
	190	
	191	
	192	
	193	

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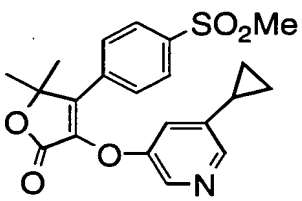
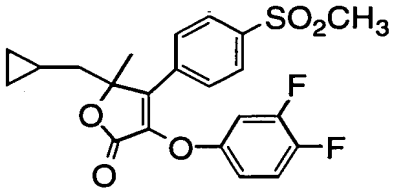
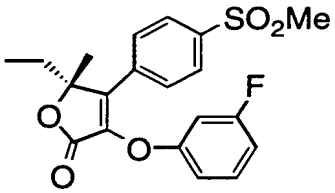
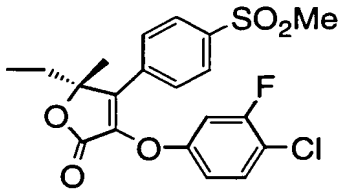
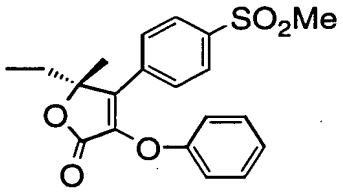
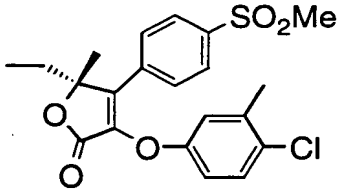
	194	
	195	H-1
	196	J
	197	J
	198	J
	199	J

Table I (continued)

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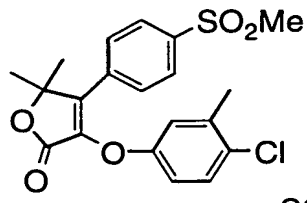
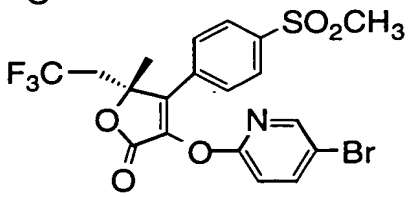
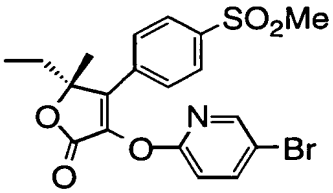
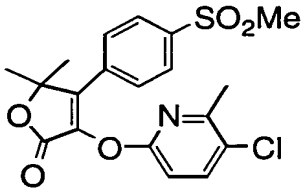
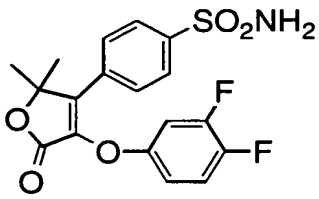
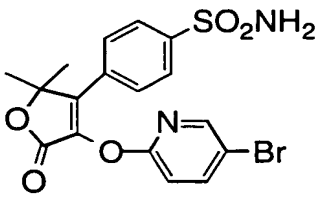
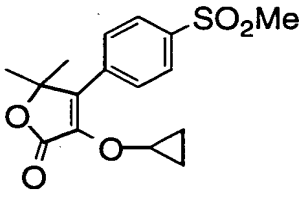
	200	L
	201	J
	202	L
	203	I-1
	204	
	205	
	206	

Table I (continued)

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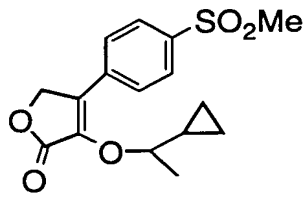
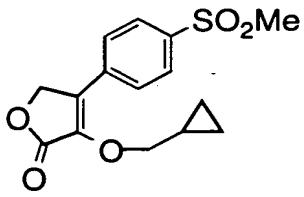
	207	L-1
	208	L-1

Assays for determining Biological Activity

The compound of Formula I can be tested using the following assays to determine their cyclooxygenase-2 inhibiting activity.

INHIBITION OF CYCLOOXYGENASE ACTIVITY

Compounds are tested as inhibitors of cyclooxygenase activity in whole cell cyclooxygenase assays. Both of these assays measure prostaglandin E_2 synthesis in response to arachidonic acid, using a radioimmunoassay. Cells used for these assays are human osteosarcoma 143 cells (which specifically express COX-2) and human U-937 cells (which specifically express COX-1). In these assays, 100% activity is defined as the difference between prostaglandin E_2 synthesis in the absence and presence of arachidonate.

Whole Cell Assays

For cyclooxygenase assays, osteosarcoma cells are cultured in 1 mL of media in 24-well multidishes (Nunclon) until confluent (1-2 x 10^5 cells/well). U-937 cells are grown in spinner flasks and resuspended to a final density of 1.5 x 10^6 cells/mL in 24-well multidishes (Nunclon). Following washing and resuspension of osteosarcoma and U-937 cells in 1 mL of HBSS, 1 µL of a DMSO solution of test compound or DMSO vehicle is added, and samples gently mixed. All assays are performed in

triplicate. Samples are then incubated for 5 or 15 minutes at 37°C, prior to the addition of arachidonic acid. Arachidonic acid (peroxide-free, Cayman Chemical) is prepared as a 10 mM stock solution in ethanol and further diluted 10-fold in HBSS. An aliquot of 10 µL of this diluted solution is added to the cells to give a final arachidonic acid concentration of 10 µM. Control samples are incubated with ethanol vehicle instead of arachidonic acid. Samples are again gently mixed and incubated for a further 10 min. at 37°C. For osteosarcoma cells, reactions are then stopped by the addition of 100 µL of 1N HCl, with mixing and by the rapid removal of the solution from cell monolayers. For U-937 cells, reactions are stopped by the addition of 100 µL of 1N HCl, with mixing. Samples are then neutralized by the addition of 100 µL of 1N NaOH and PGE_2 levels measured by radioimmunoassay.

Whole cell assays for COX-2 and COX-1 using CHO transfected cell lines

Chinese hamster ovary (CHO) cell lines which have been stably transfected with an eukaryotic expression vector pCDNAIII containing either the human COX-1 or COX-2 cDNA's are used for the assay. These cell lines are referred to as CHO [hCOX-1] and CHO [hCOX-2], respectively. For cyclooxygenase assays, CHO[hCOX-1] cells from suspension cultures and CHO[hCOX-2] cells prepared by trypsinization of adherent cultures are harvested by centrifugation (300 x g, 10 min) and washed once in HBSS containing 15 mM HEPES, pH 7.4, and resuspended in HBSS, 15 mM HEPES, pH 7.4, at a cell concentration of 1.5×10^6 cells/ml. Drugs to be tested are dissolved in DMSO to 66.7-fold the highest test drug concentration. Compounds are typically tested at 8 concentrations in duplicate using serial 3-fold serial dilutions in DMSO of the highest drug concentration. Cells (0.3×10^6 cells in 200 µl) are preincubated with 3 µl of the test drug or DMSO vehicle for 15 min at 37°C. Working solutions of peroxide-free AA (5.5 µM and 110 µM AA for the CHO [hCOX-1] and CHO [COX-2] assays, respectively) are prepared by a 10-fold dilution of a concentrated AA

solution in ethanol into HBSS containing 15 mM HEPES, pH 7.4. Cells are then challenged in the presence or absence of drug with the AA/HBSS solution to yield a final concentration of 0.5 μM AA in the CHO[hCOX-1] assay and a final concentration of 10 μM AA in the CHO[hCOX-2] assay. The reaction is terminated by the addition of 10 μl 1 N HCl followed by neutralization with 20 μl of 0.5 N NaOH. The samples are centrifuged at 300 x g at 4°C for 10 min, and an aliquot of the clarified supernatant is appropriately diluted for the determination of PGE_2 levels using an enzyme-linked immunoassay for PGE_2 (Correlate PGE_2 enzyme immunoassay kit, Assay Designs, Inc.). Cyclooxygenase activity in the absence of test compounds is determined as the difference in PGE_2 levels of cells challenged with arachidonic acid versus the PGE_2 levels in cells mock-challenged with ethanol vehicle. Inhibition of PGE_2 synthesis by test compounds is calculated as a percentage of the activity in the presence of drug versus the activity in the positive control samples.

Assay of COX-1 Activity from U937 cell microsomes

U 937 cells are pelleted by centrifugation at 500 x g for 5 min and washed once with phosphate-buffered saline and repelleted. Cells are resuspended in homogenization buffer consisting of 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA, 2 μg/ml leupeptin, 2 μg/ml soybean trypsin inhibitor, 2 μg/ml aprotinin and 1 mM phenyl methyl sulfonyl fluoride. The cell suspension is sonicated 4 times for 10 sec and is centrifuged at 10,000 x g for 10 min at 4° C. The supernatant is centrifuged at 100,000 x g for 1 hr at 4 ° C. The 100,000 x g microsomal pellet is resuspended in 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA to approximately 7 mg protein/ml and stored at -80° C.

Microsomal preparations are thawed immediately prior to use, subjected to a brief sonication, and then diluted to a protein concentration of 125 μg/ml in 0.1 M Tris-HCl buffer, pH 7.4 containing 10 mM EDTA, 0.5 mM phenol, 1 mM reduced glutathione and 1 μM hematin. Assays are performed in duplicate in a final volume of 250 μl.

Initially, 5 µl of DMSO vehicle or drug in DMSO are added to 20 µl of 0.1 M Tris-HCl buffer, pH 7.4 containing 10 mM EDTA in wells of a 96-deepwell polypropylene titre plate. 200 µl of the microsomal preparation are then added and pre-incubated for 15 min at room temperature before addition of 25 µl of 1 M arachidonic acid in 0.1 M Tris-HCl and 10 mM EDTA, pH 7.4. Samples are incubated for 40 min at room temperature and the reaction is stopped by the addition of 25 µl of 1 N HCl. Samples are neutralized with 25 µl of 1 N NaOH prior to quantitation of PGE_2 content by radioimmunoassay (Dupont-NEN or Amersham assay kits). Cyclooxygenase activity is defined as the difference between PGE_2 levels in samples incubated in the presence of arachidonic acid and ethanol vehicle.

Assay of the activity of purified human COX-2

The enzyme activity is measured using a chromogenic assay based on the oxidation of N,N,N',N'-tetramethyl-p-phenylenediamine (TMPD) during the reduction of PGG_2 to PGH_2 by COX-2 (Copeland et al. (1994) Proc. Natl. Acad. Sci. 91, 11202-11206).

Recombinant human COX-2 is purified from Sf9 cells as previously described (Percival et al (1994) Arch. Biochem. Biophys. 15, 111-118). The assay mixture (180 µL) contains 100 mM sodium phosphate, pH 6.5, 2 mM genapol X-100, 1 µM hematin, 1 mg/ml gelatin , 80-100 units of purified enzyme (One unit of enzyme is defined as the amount of enzyme required to produce an O.D. change of 0.001/min at 610 nm) and 4 µL of the test compound in DMSO. The mixture is pre-incubated at room temperature (22°C) for 15 minutes prior to initiation of the enzymatic reaction by the addition of 20 µL of a sonicated solution of 1 mM arachidonic acid (AA) and 1 mM TMPD in assay buffer (without enzyme or hematin). The enzymatic activity is measured by estimation of the initial velocity of TMPD oxidation over the first 36 sec of the reaction. A non-specific rate of oxidation is observed in the absence of enzyme (0.007 - 0.010 O.D. /min) and is subtracted before the calculation of the % inhibition. IC_{50} values are derived from 4-parameter least

squares non-linear regression analysis of the log-dose vs % inhibition plot.

HUMAN WHOLE BLOOD ASSAY

Rationale

Human whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as selective COX-2 inhibitors. Studies have shown that normal human blood does not contain the COX-2 enzyme. This is consistent with the observation that COX-2 inhibitors have no effect on PGE_2 production in normal blood. These inhibitors are active only after incubation of human whole blood with LPS, which induces COX-2. This assay can be used to evaluate the inhibitory effect of selective COX-2 inhibitors on PGE_2 production. As well, platelets in whole blood contain a large amount of the COX-1 enzyme. Immediately following blood clotting, platelets are activated through a thrombin-mediated mechanism. This reaction results in the production of thromboxane B_2 (TxB_2) via activation of COX-1. Thus, the effect of test compounds on TxB_2 levels following blood clotting can be examined and used as an index for COX-1 activity. Therefore, the degree of selectivity by the test compound can be determined by measuring the levels of PGE_2 after LPS induction (COX-2) and TxB_2 following blood clotting (COX-1) in the same assay.

Method

A. COX-2 (LPS-induced PGE_2 production)

Fresh blood is collected in heparinized tubes by venipuncture from both male and female volunteers. The subjects have no apparent inflammatory conditions and have not taken any NSAIDs for at least 7 days prior to blood collection. Plasma is immediately obtained from a 2mL blood aliquot to use as blank (basal levels of PGE_2). The remaining blood is incubated with LPS (100 µg/ml final concentration, Sigma Chem, #L-2630 from E. coli; diluted in 0.1% BSA (Phosphate buffered saline) for 5 minutes at room temperature. Five hundred µL

aliquots of blood are incubated with either 2μL of vehicle (DMSO) or 2μL of a test compound at final concentrations varying from 10nM to 30μM for 24 hours at 37 °C. At the end of the incubation, the blood is centrifuged at 12,000 x g for 5 minutes to obtain plasma. A 100μL aliquot of plasma is mixed with 400μL of methanol for protein precipitation. The supernatant is obtained and is assayed for PGE_2 using a radioimmunoassay kit (Amersham, RPA#530) after conversion of PGE_2 to its methyl oximate derivative according to the manufacturer's procedure.

B. COX-1 (Clotting-induced TxB_2 production)

Fresh blood is collected into vacutainers containing no anticoagulants. Aliquots of 500μL are immediately transferred to siliconized microcentrifuge tubes preloaded with 2μL of either DMSO or a test compound at final concentrations varying from 10nM to 30μM. The tubes are vortexed and incubated at 37°C for 1 hour to allow blood to clot. At the end of incubation, serum is obtained by centrifugation (12,000 x g for 5 min.). A 100μL aliquot of serum is mixed with 400μL of methanol for protein precipitation. The supernatant is obtained and is assayed for TxB_2 using a enzyme immunoassay kit (Cayman, #519031) according to the manufacturer's instruction.

RAT PAW EDEMA ASSAY

Protocol

Male Sprague-Dawley rats (150-200 g) are fasted overnight and are given, po, either vehicle (1% methocel or 5% Tween 80) or a test compound. One hr later, a line is drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume (V_0) is measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals are then injected subplantarly with 50 μl of 1% carrageenan solution in saline (FMC Corp, Maine) into the paw using an insulin

syringe with a 25-gauge needle (i.e. 500 µg carrageenan per paw). Three hr later, the paw volume (V_3) is measured and the increases in paw volume ($V_3 - V_O$) are calculated. The animals are sacrificed by CO_2 asphyxiation and the absence or presence of stomach lesions scored. Data is compared with the vehicle-control values and percent inhibition calculated. All treatment groups are coded to eliminate observer bias.

NSAID-INDUCED GASTROPATHY IN RATS

Rationale

The major side effect of conventional NSAIDs is their ability to produce gastric lesions in man. This action is believed to be caused by inhibition of Cox-1 in the gastrointestinal tract. Rats are particularly sensitive to the actions of NSAIDs. In fact, rat models have been used commonly in the past to evaluate the gastrointestinal side effects of current conventional NSAIDs. In the present assay, NSAID-induced gastrointestinal damage is observed by measuring fecal ^{51}Cr excretion after systemic injection of ^{51}Cr-labeled red blood cells. Fecal ^{51}Cr excretion is a well-established and sensitive technique to detect gastrointestinal integrity in animals and man.

Methods

Male Sprague Dawley rats (150 - 200 g) are administered orally a test compound either once (acute dosing) or b.i.d. for 5 days (chronic dosing). Immediately after the administration of the last dose, the rats are injected via a tail vein with 0.5 mL of ^{51}Cr-labeled red blood cells from a donor rat. The animals are placed individually in metabolism cages with food and water ad *lib*. Feces are collected for a 48 h period and ^{51}Cr fecal excretion is calculated as a percent of total injected dose. ^{51}Cr-labeled red blood cells are prepared using the following procedures. Ten mL of blood is collected in heparinized tubes via the vena cava from a donor rat. Plasma is removed by centrifugation and replenished with equal volume of HBSS. The red blood cells are incubated with 400 Ci of sodium ^{51}chromate for 30 min. at 37C. At the end of the incubation, the

red blood cells are washed twice with 20 mL HBSS to remove free sodium ^{51}chromate. The red blood cells are finally reconstituted in 10 mL HBSS and 0.5 mL of the solution (about 20 Ci) is injected per rat.

PROTEIN-LOSING GASTROPATHY IN SQUIRREL MONKEYS

Rationale

Protein-losing gastropathy (manifested as appearance of circulating cells and plasma proteins in the GI tract) is a significant and dose-limiting adverse response to standard non-steroidal anti-inflammatory drugs (NSAIDs). This can be quantitatively assessed by intravenous administration of $^{51}CrCl_3$ solution. This isotopic ion can avidly bind to cell and serum globins and cell endoplasmic reticulum. Measurement of radioactivity appearing in feces collected for 24 h after administration of the isotope thus provides a sensitive and quantitative index of protein-losing gastropathy.

Methods

Groups of male squirrel monkeys (0.8 to 1.4 kg) are treated by gavage with either 1% methocell or 5% Tween 80 in H_2O vehicles, (3mL/kg b.i.d.) or test compounds at doses from 1 - 100 mg/kg b.i.d. for 5 days. Intravenous ^{51}Cr (5Ci/kg in 1 ml/kg phosphate buffer saline (PBS)) is administered 1 h after the last drug/vehicle dose, and feces collected for 24 h in a metabolism cage and assessed for excreted ^{51}Cr by gamma-counting. Venous blood is sampled 1 h and 8 h after the last drug dose, and plasma concentrations of drug measured by RP-HPLC.

Representative Biological Data

Compounds of the present invention are inhibitors of cyclooxygenase-2 and are thereby useful in the treatment of cyclooxygenase-2 mediated diseases as enumerated above. The activities of the compounds against cyclooxygenase may be seen in the representative results shown below. In the assay, inhibition is determined

by measuring the amount of prostaglandin E_2 (PGE_2) synthesized in the presence of arachidonic acid, cyclooxygenase-1 or cyclooxygenase-2 and a putative inhibitor. The IC_{50} values represent the concentration of putative inhibitor

required to return PGE_2 synthesis to 50% of that obtained as compared to the uninhibited control.

The results for certain of the biological assays may be seen in Tables II, III and IV.

Table II

Example	Rat Paw Edema ED_{50}(mg/kg)
1	0.14
2	2.4
6	7.65
25	0.74

T1320X

T1330X

Table III

	COX-2 (IC50)			COX-1 (IC50)		
Example	TMPD	CHO	HWB	U937	CHO	HWB
	uM	uM	uM	uM	uM	uM
1	1.1	0.02	0.063	0.99	>50	9.2
2	0.2	0.02	0.074	3.0	>50	23.0
3	1.0	0.04	0.18	1.0	>50	6.1
4	0.62	0.01	0.04	1	>50	5
5	3.3	0.02	0.04	0.3		
6	2.0	0.01	0.02	0.4		1.8
7	1.4	0.009		1		
8	4.6	0.02	<0.41	0.3		
9	0.5	0.19	0.90	>10		>100
10	4.9		18.6	>10		
11	0.6	0.09	1.53	>30	>50	
12	14.7	3.52	4.5	>10		
13	64.4	0.118	2.65	>10		
14	10.8	0.1	<0.04	>10	>50	58.3
15	0.22	0.81	>30	>10	>50	
16	1.8		2.6	>10		>90
17	>100		.30	>10		
18	5.51		>30	>30		
19b	16.9	0.57	0.84	>10	>50	>90
20	0.44	0.03	0.23	0.3	4.68	
21	0.47	0.23	1.04	>10		
22	0.2		9.66	>1		
23	1.33	.5	1.53	>30	>50	
24c	3.0	0.03	<0.41	>3		25.3
25	4.7	0.02	<0.41	3	24	
26	35	0.12	0.12	~10	>100	
27	14	0.41	2.3	>10	>100	
29	3.6	0.015	1.0	1		

T1340X

Table IV

	COX-2(IC_{50}, μM)			COX-1 (IC_{50}, μM)	Rat Paw Edema ED_{50}(mg/kg)
Example	TMPD	CHO	HWB	CHO	
32	2.0	0.02	0.08		
37	>100	0.27	1.0	>50	-
38	41	0.49	0.52	>50	-
39	3.3	0.92	0.08		
45	11	>5	1.8		-
48	33	0.04	0.08		-
49	7.8	0.2	0.61		-
51	>100	0.67	0.26		-
53	47	>5	3.0		-
55	43	1.8	1.2		-
56		>5	4.8		-
57	54	2.0	23		-
58	6.4	0.04	0.08	>50	0.32
108	3.7	0.02	0.03	>50	0.68
109	11	0.04	0.4	>50	0.8
110	11	>5	3.0		-
111	>100	>5	15		
112	28	0.03	0.04		8.0
113	8.7	0.03	<0.41		-
115	2.2	0.18	0.9		-
116	15	0.34	<0.41		-
117	0.95	0.02	0.02		1.0
118	2.2	0.008	0.05		1.4
119	>100	0.47	<0.41		-

Table IV - cont'd

	COX-2(IC_{50}, μM)			COX-1 (IC_{50}, μM)	Rat Paw Edema ED_{50}(mg/kg)
Example	TMPD	CHO	HWB	CHO	
120	42		4.5		-
121	1.6	0.09	0.45		10
122	4.6	0.15	0.38		1.2
123	11	0.09	<0.41		-
124	6.3	0.03	<0.41		-
125	>100	>5			
127	5.8	0.04	0.04		-
128	1.7	0.01	<0.41		5.0
129	5.4	0.15	<0.41		-
130	7.9	0.03	<0.4`		-
133	7.1	0.04	<0.41		-
134		0.04	0.08		0.9
136			1.3		
137		0.55	5.2		-
140		0.12	0.54		4.6
141		0.03	<0.41		-
143	3.1		<0.41		-
144	2.9		<0.41		-
146			0.10		-
147			0.11		-
148		0.01	0.14		1.2
149	5.6	0.02	0.07		0.9
150	2.1	0.01	0.02		-
31	7.5	0.37	0.66		-
50	24	0.09	0.24		-

Table IV - cont'd

	COX-2(IC_{50}, μM)			COX-1 (IC_{50}, μM)	Rat Paw Edema ED_{50}(mg/kg)
Example	TMPD	CHO	HWB	CHO	
159	25	0.07	0.26		-
160	3.20	0.35	3.6		-
161	>100	2.9	1.7		-
162	8.0	0.06	0.62		-
163	6.6	0.02	0.09		0.64
164	>100	0.20	0.55		2.0
165	>100	2.0	4.5		-
166	6.5	0.05	0.28		4.9
167		0.11	0.21		6.4
168	3.0	0.05	1.1	29	1.0
169	4.0	0.05	<0.41		4.6
170		0.33	2.0		-
171			0.46		-
173			<0.41		-
174	5.8	0.02	<0.41		1.6
175	9.5	0.05	2.3		-
176	2.2	0.03	0.08		-
177	6.5	0.04	<0.41		-
178		0.04	<0.41		-
179			2.7		-
180			0.41		
181			<0.41		-
184		0.04	<0.41		-
185		0.39	2.2		-

Table IV - cont'd

	COX-2(IC_{50}, μM)			COX-1 (IC_{50}, μM)	Rat Paw Edema ED_{50}(mg/kg)
Example	TMPD	CHO	HWB	CHO	
186		1.4	6.5		-
188		0.02	0.09		-
189		0.05	0.28		-
191		0.98	4.3		-
192		0.02	<0.41		-
195		0.02	<0.41		-
196		0.04	0.48		-
197		0.02	<0.41		-
198		0.06	0.17		-
199		0.11	0.87		-
200		0.16	0.13		-
201	14	0.07	0.18		2.7
202	13	0.04	<0.41		5.4
203		0.17	0.94		

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C;

(ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;

(iv) melting points are uncorrected and `d' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data;

(vi) yields are given for illustration only;

(vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), M.P. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

EXAMPLE 1

3-(3,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-Methyl-1-(4-(methylthio)phenyl)-propan-1-one

To a suspension of aluminum chloride (136 g, 1.02 mol) in chloroform (1.0 L) cooled to -10 °C, was added dropwise isobutyrylchloride (115 mL, 1.10 mol). Then thioanisole (100 mL, 0.85 mol) was added dropwise. Upon completion of addition the reaction was allowed to proceed at r.t. for 1.5h. The reaction was cooled to 10 °C and quenched by addition of water (750 mL). The organic layer was separated, washed with water (2 x 500 mL), saturated $NaHCO_3$ solution(2 x 500 mL), brine (1 x 500 mL), and then dried over Na_2SO_4. After concentration *in vacuo*., the resulting crude product crystallized upon standing under high vacuum for 30 min to give the title compound as a brown solid.

Step 2: 2-Hydroxy-2-methyl-1-(4-(methylthio)phenyl)propan-1-one

To a solution of 2-methyl-1-(4-(methylthio)phenyl)propan-1-one (28.5 g, 147 mmol, Step 1), Aliquat 336 (11.0 mL, 24 mmol) and carbon tetrachloride (21 mL, 218 mmol) in toluene (43 mL) was added sodium hydroxide (12.9 g, pellets, 322 mmol). The reaction was stirred at 15 °C for 2h and then at r.t. for 16h. The reaction was diluted with water (100 mL), brine (100 mL) and EtOAc (300 mL). The aqueous phase was acidified with 1 N HCl and extracted with EtOAc (100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography eluted with 15% EtOAc in hexane to give the title compound as a thick syrup.

Step 3: 2-Hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one

To a cold (4 °C) solution of 2-hydroxy-2-methyl-1-(4-(methylthio)phenyl)propan-1-one (45.0 g, 214 mmol, Step 2) in t-butanol (500 mL) and CH_2Cl_2 (500 mL) was added a solution of OXONE™ (194 g, 316 mmol) in water (1.4 L). The resulting suspension was stirred at r.t. for 18h. The reaction was diluted with EtOAc (400 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 250 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was dissolved in diethyl ether (250 mL), hexane was added (150 mL) and the product was swished for 2h. The product was collected by filtration to give the title compound as a yellow solid.

Step 4: 3-(3,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

A solution of 3,4-difluorophenoxyacetic acid (0.51g, 2.73 mmol), 2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one (0.5g, 2.1mmol, Step 3), CMC (1.13g, 2.73mmol) and DMAP (15 mg, 0.10mmol) in dichloromethane (12ml) was stirred at r.t. for 18 hrs. Then, DBU (0.63ml, 4.2mmol) was added and the reaction mixture was refluxed for 3 h. After cooling to r.t.the mixture was extracted with ethyl acetate and washed successively with water, 1N HCl and brine. The organic layer was dried over $MgSO_4$, filtered and the solvent evaporated under vacuum.The residue was triturated in a mixture of ethyl acetate and hexane affording the title compound as a solid. M.P.: 93-95 °C.
^1H NMR (CD_3COCD_3) δ 1.77 (6H, s), 3.15 (3H, s), 6.93-6.97 (1H, m), 7.12-7.29 (2H, m), 7.92 (2H, d), 8.04 (2H, d).
Analysis calculated for $C_{19}H_{16}F_2O_5S$: C, 57.86; H, 4.09;
Found: C, 57.77; H, 4.28

EXAMPLE 2

3-(3-Fluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 1, the title compound was prepared from 3-fluorophenoxyacetic acid. M.P.: 136-138°C.

^{1}H NMR (CD_3COCD_3) δ 1.79 (6H, s), 3.15 (3H, s), 6.85-6.94 (3H, M), 7.31-7.86 (1H, m), 7.93 (2H, d), 8.03 (2H,d).

EXAMPLE 3

3-(3,5-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 1, the title compound was prepared from 3,5-difluorophenoxyacetic acid. M.P.: 159-161°C.

^{1}H NMR (CD_3COCD_3) δ 1.80 (6H, s), 3.17 (3H, s), 6.78-6.84 (3H, m), 7.96 (2H, d), 8.06 (2H, d).

Analysis calculated for $C_{19}H_{16}F_2O_5S$: C, 57.86; H, 4.09;
Found: C, 57.66; H, 4.30

EXAMPLE 4

3-Phenoxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 3-Phenoxy-5,5-dimethyl-4-(4-(methylthio)phenyl)-5H-furan-2-one

Following the procedure described for example 1, Step 4, the title compound was prepared from phenoxyacetic acid and 2-hydroxy-2-methyl-1-(4-(methylthio)phenyl)propan-1-one (example 1, Step 4).

^{1}H NMR (CD_3COCD_3) δ 1.79 (6H, s), 2.51 (3H, s), 7.03-7.10 (3H, m), 7.30-7.37 (4H, m), 7.72 (2H, d).

Step 2: 3-Phenoxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

The compound obtained in Step 1 (150 mg, 0.46mmol) was stirred in dichloromethane (5mL) with 3-chloroperoxybenzoic acid (250 mg, 1.38mmol) for 18 hrs. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate, brine, dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. The residue was triturated in Et_2O to afford the title compound. M.P.: 135-136°C. ^1H NMR (CD_3COCD_3) δ 1.78 (6H, s), 3.14 (3H, s), 7.05-7.08 (3H, m), 7.28-7.30 (2H, m), 7.92 (2H, d), 8.01 (2H, d).

Analysis calculated for $C_{19}H_{18}O_5S$: C, 63.67; H, 5.06; S, 8.95;
Found: C, 64.02; H, 5.10: S, 8.84

EXAMPLE 5

3-(2,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-Bromoacetic acid, 2-methyl-1-(4-(methylsulfonyl) phenyl)propan-1-one ester

To a 0°C solution of 2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one (4.0g, 16.5mmol, example 1, Step 3) in dichloromethane (100mL) was added pyridine (23.5mL, 291mmol) and bromoacetyl bromide (24.9mL, 285.3mmol) portionwise over 2 hrs. The reaction mixture was allowed to warm to r.t. and stirred for a further hour. The mixture was diluted with dichloromethane, washed with 1N HCl, brine, filtered through cotton and the solvent was evaporated under vacuum. Purification by silica gel chromatography (40% EtOAc/Hex.) provided 3.50g of the title compound.

^1H NMR (CD_3COCD_3) δ 1.75 (6H, s), 3.20 (3H, s), 4.00 (2H, s), 8.05 (2H, m), 8.25 (2H, m).

Step 2: 2-(2,4-Difluorophenoxy)acetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one-2-yl ester

Sodium hydride, 60% dispersion (66mg, 1.66mmol), was rinsed with hexane, suspended in 7mL of DMF and cooled to 0°C. To this suspension was added 2,4-difluorophenol (170μL, 1.79mmol). After 5 minutes at 0°C, 2-bromoacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (Step 1) (233mg, 1.79mmol) was added and the reaction mixture was stirred for 30 minutes. Dichloromethane was added and the mixture was washed with 1N HCl and the organic solvent was evaporated under vacuum. The residue was dissolved in 25%EtOAc/Et_2O and washed with 1N NaOH, water (2X) brine and dried over $MgSO_4$. After filtration and evaporation of the solvent under vacuum 470mg of the title compound was obtained.
^1H NMR (CD_3COCD_3) δ 1.75 (6H, s), 3.20(3H, s), 4.80 (2H, s), 6.60 (1H, m), 6.75 (1H, m), 7.00 (1H, m), 8.05 (2H, m), 8.20 (2H, m).

Step 3: 3-(2,4-Difluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

To a solution of 2-(2,4-difluorophenoxy)acetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one-2-yl ester (Step 2) (470 mg, 1.14mmol) in acetonitrile (7mL) was added DBU (187μL, 1.25mmol) and the resulting solution was heated at 50 °C for 20 minutes. After cooling to r.t. dichloromethane was added and the mixture was washed with 1 N HCl, brine, filtered over cotton and the solvent evaporated under vacuum. Purification by silica gel chromatography followed by a swish in EtOAc/Et_2O afforded 122 mg of the title compound.
^1H NMR (CD_3COCD_3) δ 1.70 (6H, s), 3.15 (3H, s), 6.90 (1H, m), 7.10 (1H, m), 7.30 (1H, m), 7.85 (2H, m), 8.00 (2H, m).

EXAMPLE 6

3-(4-Chlorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 1, the title compound was prepared from 4-chlorophenoxyacetic acid. M.P.: 113-114 °C

^{1}H NMR (CD_3COCD_3) δ 1.77 (6H, s), 3.15 (3H, s), 7.11 (2H, d), 7.31 (2H, d), 7.91 (2H, d), 8.04 (2H, d)

EXAMPLE 7

3-(3,4-Dichlorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 1, the title compound was prepared from 3,4-dichlorophenoxyacetic acid. M.P.: 144-145°C.

^{1}H NMR (CD_3COCD_3) δ 1.78 (6H, s), 3.15 (3H, s), 7.12-7.15 (1H, m), 7.35-7.36 (1H, s), 7.49 (1H, d), 7.92 (2H, d), 8.04 (2H, d).

EXAMPLE 8

3-(4-Fluorophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 1, the title compound was prepared from 4-fluorophenoxyacetic acid.

^{1}H NMR (CD_3COCD_3) δ 1.76 (6H, s), 3.14 (3H, s), 7.02-7.13 (4H, m), 7.91 (2H, d), 8.01 (2H, d).

EXAMPLE 9

3-(4-Fluorophenylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 1, the title compound was prepared from 4-fluorophenylthioacetic acid.
^{1}H NMR ($CDCl_3$) δ 1.55 (6H, s), 3.08 (3H, s), 6.85 (2H, m), 7.26 (2H, m), 7.35 (2H, d), 7.94 (2H, d)

EXAMPLE 10

3-(3,5-Difluorophenylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

To a mixture of 3,5-difluorothiophenol (1.0g) and methyl bromoacetate (1.2g) in methanol (20mL) was added 2mL of a solution of NaOH (0.69mL of 10N in 3mL of water), the mixture was stirred for 1h, then 2mL of 10N NaOH was added and the mixture stirred for another hour. The solvent was evaporated under vacuum, the residue taken in water and washed with Et_2O, then acidified with 1N HCl and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$, filtered and the solvent evaporated under vacuum giving 850mg of 3,5-difluorophenylthioacetic acid. This acid was reacted as in Step 1 to afford the title compound.
^{1}H NMR ($CDCl_3$) δ 1.60 (6H, s), 3.10 (3H, s), 6.60-6.80 (3H, m), 7.45 (2H, d), 8.00 (2H, d).

EXAMPLE 11

3-Phenylthio-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 1, the title compound was prepared from phenylthioacetic acid. M.P.: 98-114°C.
^{1}H NMR (CD_3COCD_3) δ 1.61 (6H, s), 3.16 (3H, s), 7.21-7.30 (5H, m), 7.61 (2H, d), 7.96 (2H, d).
Analysis calculated for $C_{19}H_{18}O_4S_2$: C, 60.94; H, 4.84; S, 17.12;

Found: C, 61.01; H, 4.90: S, 16.94

EXAMPLE 12

3-(N-Phenylamino)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-Phenylaminoacetic acid 2-methyl-1-(4-(methylsulfonyl) phenyl)propan-1-one ester

Following the procedure described in example 13 Step 1 but using aniline the title compound was obtained.
^{1}H NMR (CD_3COCD_3) δ 1.70 (6H, s), 3.15 (3H, s), 3.95 (2H, br s), 5.15 (1H, br s), 6.40 (2H, m), 6.55 (1H, m), 7.00 (2H, m), 8.00 (2H, m), 8.25 (2H, m).

Step 2: 3-N-Phenylamino-5,5-dimethyl-4-(4-(methylsulfonyl)-phenyl)-5H-furan-2-one

Following the procedure described in example 13 Step 2 but using 2-phenylaminoacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl) propan-1-one ester the title compound was obtained.
^{1}H NMR (CD_3COCD_3) δ 1.65 (6H, s), 3.05 (3H, s), 6.70 (3H, m), 6.95 (2H, m), 7.25 (1H, br s), 7.50 (2H, m), 7.75 (2H, m).

EXAMPLE 13

3-(N-Methyl-N-phenylamino)-5,5-dimethyl-4-(4-(methylsulfonyl)-phenyl)-5H-furan-2-one

Step 1: 2-(N-Phenyl-N-methylamino)acetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester

To a solution of 2-bromoacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (example 5, Step1) (1.0g, 2.75mmol) in toluene (2.5mL) was added N-methylaniline (3.0mL, 27.5mmol) and the resulting solution was heated at 115°C for 16 hrs.

After cooling to r.t. the reaction mixture was washed with brine and filtered through cotton. Purification by silica gel chromatography provided 850mg of the title compound.

Step 2: 3-(N,-Methyl-N-phenylamino)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

To a solution of 2-(N-phenyl-N-methylamino)acetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (700mg, 1.80mmol) in acetonitrile (3mL) was added DBU (2.7mL, 18.0mmol) and the resulting solution was heated at 60°C for 1 h. After cooling to r.t. dichloromethane was added and the mixture was washed with 1N HCl, brine and filtered through cotton and the solvent was evaporated under vacuum. Purification by silica gel chromatography followed by swish in EtOAc/Hex. afforded 266mg of the title compound.

^{1}H NMR (CD_3COCD_3) δ 1.70 (6H, s), 3.05 (3H,s), 3.15 (3H, s), 6.70 (1H, m), 6.80 (2H, m), 7.10 (2H, m), 7.65 (2H, m), 7.90 (2H, m)

EXAMPLE 14

3-Cyclohexyloxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-Bromo-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one

To a solution of 2-methyl-1-(4-(methylthio)phenyl)propan-1-one (example, 1, Step 1) (417.94g) in ethyl acetate (1.2L) and cyclohexane (1.7L) was added bromine (110mL) portionwise. After stirring for 10 min the mixture was washed with water, saturated sodium bicarbonate and brine. To this mixture was then added sodium tungstate (6.7g), Aliquat 336 (25g) and water (200 mL). The mixture was then heated to 50°C and hydrogen peroxide (30%, 600mL) was added slowly. Ethyl acetate and water were then added to the mixture and the organic layer separated, washed with water, dried over sodium sulfate, filtered and the title compound crystalized and was collected by filtration.

Step 2: 2-Cyclohexyloxyacetic acid 2-methyl-1-(4-(methylsulfonyl) phenyl)propan-1-one ester

A solution of 2-cyclohexyloxyacetic acid (1.74g, 11mmol), 2-bromo-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one (3.05g, 10mmol) and diisopropylethylamine (2.20g, 17mmol) in 30mL of ethanol was refluxed for 15 h. The solvent was evaporated and the residue dissolved in water and extracted with EtOAc, washed with 5% HCl, saturated sodium bicarbonate, brine and dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. Purification by silica gel chromatography afforded 3.0g of the title compound.

Step 3: 3-Cyclohexyloxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

A solution of the ester from the previous step (492 mg, 1.29mmol) and DBU (1mL) in 5mL of acetonitrile was heated at reflux for 15h.. To the cooled solution was added 5% HCl and the mixture was extracted with EtOAc, washed with a saturated solution af ammonium chloride and dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. Purification by silica gel chromatography afforded the title compound.M.P.: 143-144°C

^1H NMR (CD_3COCD_3) δ 1.20-1.35 (3H, m), 1.40-1.50 (3H, m), 1.66 (6H, s), 1.60-1.70 (2H, m), 1.85-1.95 (2H, m), 3.20 (3H, s), 4.85 (1H, m), 8.00-8.10 (4H, m)

Analysis calculated for $C_{19}H_{24}O_5S$: C, 62.62; H, 6.64;
Found: C, 62.28; H, 6.57

EXAMPLE 15

3-Phenylthio-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

At 0°C, triethylamine (335 µL) was added to a solution of thiophenoxyacetic acid (161 mg) and 2-bromo-1-(4-(methylsulfonyl)phenyl) ethanone (272 mg, WO 9500501, example 9, Step 1) in 5mL of acetonitrile and the mixture was stirred at 0°C for 1h.

The reaction mixture was then cooled to -20°C and DBU (265 µL) was added. The mixture was stirred for 30 min. at -20°C and was quenched by addition of 1N HCl. The product was extracted with EtOAc, dried over sodium sulfate and partially purified by silica gel chromatography. The impure product was recrystalized from EtOAc/Hexane to afford the title compound as a solid

^{1}H NMR ($CDCl_3$) δ 3.10 (3H, s), 5.25 (2H, s), 7.24-7.38 (5H, m), 7.93 (2H, d), 8.03 (2H, d).

Analysis calculated for $C_{17}H_{14}O_4S_2$: C, 58.94; H, 4.07;
Found: C, 58.88; H, 4.18

EXAMPLE 16

3-Benzyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 3-Phenylpropanoic acid 2-methyl-1-(4-(methylthio)phenyl) propan-1-on-2-yl ester

To a -30 °C solution of 2-hydroxy-2-methyl-1-(4-(methylthio)phenyl)propan-1-one (1.05g, example 1, Step 2) in dichloromethane (20mL) was added 3-phenylpropionyl chloride (1.68g) in dichloromethane (10 mL) followed by pyridine (791mg) and the mixture was allowed to warm up slowly to 25°C and stirred for 12 h. Ethyl acetate was added to the mixture and it was washed with 1N HCl, brine, dried over magnesium sulfate filtered and the solvent was evaporated under vacuum. Purification by silica gel chromatography afforded 1.36g of the title compound.

^{1}H NMR (CD_3COCD_3) δ 1.65 (6H, s), 2.50 (3H, s), 2.55-2.65 (2H, t), 2.75-2.85(2H, t), 7.10-7.40 (7H, m), 7.90-8.00 (2H, d)

Step 2: 3-Benzyl-5,5-dimethyl-4-(4-(methylthio)phenyl)-5H-furan-2-one

To a 0°C solution of the ester from the previous step (1.14g) in DMF (10mL) and THF (2mL) was added sodium hydride (120mg of 80% dispersion) and the mixture was stirred for 2 h at 25°C. Then it was

poured over icy 1N HCl and extracted with ethyl acetate , the organic layer was washed with water, brine, dried over $MgSO_4$ and the solvent evaporated under vacuum. The residue was purified by silica gel chromatography affording 596 mg of the title compound.
^1H NMR (CD_3COCD_3) δ 1.50 (6H, s), 2.55 (3H, s), 3.50 (2H, s), 7.05-7.30 (7H, m), 7.35-7.40 (2H, d)

Step 3: 3-Benzyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

To a 0°C solution of the lactone from the previous step (596mg) in dichloromethane (10 mL) and methanol (5mL) was added portionwise MMPP (2x590mg) and the mixture was allowed to slowly warm-up to 25°C. After 2h. at 25°C the mixture was partitioned between dichloromethane and water, the organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. The residue was swished in ether to yield 530mg of the title compound.
Analysis calculated for $C_{20}H_{20}O_4S$: C, 67.40; H, 5.65;
Found: C, 67.28; H, 5.78

EXAMPLE 17

3-(3,4-Difluorophenylhydroxymethyl)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

Using a procedure similar to the Steps 1, 2 and 3 of example 19 but using 3,4-difluorobenzaldehyde as an electrophile the title compound was obtained.
^1H NMR (CD_3COCD_3) δ 1.45 (6H, s), 3.15 (3H, s), 5.00 (1H, bs), 5.50 (1H, bs), 6.45-6.55 (2H, d), 7.00-7.30 (3H, m), 7.95-8.05 (2H, d).

EXAMPLE 18

3-(3,4-Difluorobenzoyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Using a procedure similar to Step 4 of example 19 and using the compound obtained in example 17, the title compound was obtained ^{1}H NMR (CD_3COCD_3) δ 1.75 (6H, s), 3.10 (3H, s), 7.35-7.45 (1H, m), 7.65-7.75 (2H, d), 7.75-7.90 (2H, m), 7.95-8.05 (2H, d).

EXAMPLE 19

3-Benzoyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: Acetic acid 2-methyl-1-(4-methylthiophenyl)propan-1-on-2-yl ester

To a 0°C solution of 2-hydroxy-2-methyl-1-(4-(methylthio)phenyl)propan-1-one (150g, example 1, Step 2), DBU (217g) and DMAP (7g) in dichloromethane (850mL) was added acetyl chloride (112.2g) dropwise and the mixture was stirred for 6 h. at 25°C. More DBU (32.5g) was added and the mixture was stirred an additionnal 16 h. The reaction mixture was poured over 2N HCl (800mL) and the organic layer was separated, washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent was evaporated under vacuum. The residue was swished in Et_2O, then 25% ethyl acetate in hexane, then filtered and dried giving 74g of the title compound.
^{1}H NMR (CD_3COCD_3) δ 1.60 (6H, s), 1.90 (3H, s), 2.55 (3H, s), 7.30 (2H, d), 8.00 (2H, d).

Step 2: 5,5-Dimethyl-4-(4-(methylthio)phenyl)-5H-furan-2-one

To a 0-5°C solution of the ester from the previous step (74g) in DMF (1.2L) was added NaH (9g, 80% dispersion) portionwise and the mixture was stirred for 3 h. Saturated aquous NH_4Cl was added slowly . The mixture was then partitioned between ethyl acetate and water, the organic layer was washed with water, dried with Na_2SO_4, filtered and the solvent was evaporated under vacuum. The residue was swished in 30% ethyl acetate/ hexane to yield the title compound (38g).
^{1}H NMR (CD_3COCD_3) δ 1.70 (6H, s), 2.55 (3H, s), 6.40 (1H, s), 7.40 (2H, d), 7.70 (2H, d).

Step 3: 5,5-Dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(phenylhydroxymethyl) -5H-furan-2-one

To a -78°C solution of the lactone (702mg) obtained in the previous step in THF was added 0.67M LDA (9.25mL) and the mixture was reacted for 5min. Benzoyl chloride (913mg) was then added at -78°C and after 15 min the mixture was poured over icy 1N HCl. The organic material was extracted with ethyl acetate, washed with brine, dried with $MgSO_4$, filtered and the solvent was evaporated under vacuum.The residue was dissolved in dichloromethane (10mL) and methanol (10mL) and the solution cooled to 0°C. MMPP (4.9g) was added and the mixture warmed and stirred at 25°C for 2h. The mixture was poured over icy water and the organic layer was dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. The residue was purified by silica gel chromatography to yield 190 mg of compound which was dissolved in methanol(2mL) and THF (1mL), cooled to 0°C and a catalytic amount of NaOH was added. The mixture was poured in icy water and extracted with ethyl acetate, the organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent evaporated under vacuum.

Step 4: 3-Benzoyl-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

The residue was dissolved in acetone (3mL), and Jone's reagent (3M, 150µL) was added. The mixture was stirred for 1h. then poured over icy water and extracted with ethyl acetate, the organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated under vacuum. The residue was swished in ether to yield the title compound (123mg).

Analysis calculated for $C_{20}H_{18}O_5S$: C, 64.85; H, 4.84;
Found: C, 64.63; H, 5.23

EXAMPLE 20

4-(4-(Methylsulfonyl)phenyl)-3-phenoxy-1-oxaspiro[4.4]non-3-en-2-one

Using a procedure similar to the one used in example 1 but using (1-hydroxycyclopentyl)-(4-(methylsulfonyl)phenyl)methanone from example 21, Step 3 and phenoxyacetic acid the title compound was obtained.

^{1}H NMR ($CDCl_3$) δ 1.80-2.30 (8H, m), 3.04 (3H, s), 6.95-7.35 (5H, m), 7.75 (2H, d), 7.95 (2H, d).

EXAMPLE 21

4-(4-(Methylsulfonyl)phenyl)-3-phenylthio-1-oxaspiro[4.4]non-3-en-2-one

Step 1: Cyclopentyl-(4-(methylthio)phenyl)methanone

To a suspension of anhydrous aluminum chloride (9.3 g, 69.6 mmol) in 58 mL $CHCl_3$ at 0 °C was added dropwise cyclopentanecarbonyl chloride (10.0 g, 75.4 mmol), followed by thioanisole (7.21 g, 58.0 mmol). The ice bath was removed and the mixture was stirred at room temperature for 2h. Water (200 ml) was added with cooling, the layers were separated and the aqueous layer was extracted with $CHCl_3$ (3 x 50 mL). The combined aqueous layers were dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel (4% EtOAc/hexane) to give 11.9 g of the title ketone (93%).

^{1}H NMR (CD_3COCD_3) δ 7.94 (d, 2H), 7.36 (d, 2H), 3.79 (q, 1H), 2.56 (s, 3H), 2.00-1.71 (m, 4H), 1.70-1.50 (m, 4H).

Step 2: (1-Hydroxycyclopentyl)-(4-(methylthio)phenyl)methanone

To a solution of the ketone from Step 1 (7.2 g, 32.7 mmol) in 4.7 ml CCl_4 and 9.6 ml toluene was added Aliquat 336 (2.11 g, 5.20 mmol) and powdered NaOH (2.88 g, 71.9 mmol) and the mixture was stirred for 16h at r.t. To the brown mixture was added 100 ml of 5% aq.

HCl and extracted with EtOAc (4 x 100 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Chromatography on silica gel (20% EtOAc/hexane) gave 5.4 g of the title compound as a white waxy solid (70%).

^1H NMR (CD_3COCD_3) δ 8.11 (d, 2H), 7.31 (d, 2H), 4.63 (s, 1H, disappears by D_2O wash), 2.56 (s, 3H), 2.24 (m, 2H), 1.89 (m, 4H), 1.71 (m, 2H).

Step 3: (1-Hydroxycyclopentyl)-(4-(methylsulfonyl)phenyl)-methanone

The sulfide obtained in Step 2 (56g) was dissolved in dichloromethane (800 mL) and methanol (200 mL) and treated with MMPP (139 g) and stirred for 3 h. The organic layer was diluted with dichloromethane, washed with water and brine, dried over $MgSO_4$, filtered and the solvent evaporated to afford the title compound.

Step 4: 4-(4-(Methylsulfonyl)phenyl)-3-phenylthio-1-oxaspiro [4.4]non-3-en-2-one

The hydroxyketone from the previous step was reacted with phenylthioacetic acid as in the procedure for example 1, Step 4 to afford the title compound.

^1H NMR ($CDCl_3$) δ 1.70-2.05 (8H, m), 3.06 (3H, s), 7.10-7.25 (5H, m), 7.35 (2H, d), 7.90 (2H, d).

EXAMPLE 22

4-(2-Oxo-3-phenylthio-1-oxa-spiro[4,4]non-3-en-4-yl)benzene-sulfonamide

To a solution of 1-(hydroxycyclopentyl)-(4-methylthiophenyl) methanone (52g, example 21, Step 2) in CH_2Cl_2 (400 mL) and methanol (200mL) at 0°C was added portionwise MMPP (61g). After stirring for 3 h the reaction mixture was washed with water, dried over Na_2SO_4, filtered and evaporated to dryness to provide the sulfoxide intermediate which (7.56g) was dissolved in TFAA (100.0 mL) and

refluxed for 3 h. The mixture was cooled to 0°C and 10N NaOH (24mL), was added dropwise and under nitrogen. After vigorous stirring for 0.5h, acetic acid (100mL) and water (20mL)was added. The mixture was cooled to 0°C and chlorine gas was bubbled for 20min. The excess chlorine was removed under vacuum and the mixture was poured over icy water and extracted with ethyl acetate. The extracts were washed with water, saturated $NaHCO_3$ and brine . The organic layer was cooled to 0°C and *t*-butylamine (10mL) was added and stirred for 1h. The reaction mixture was diluted with water and neutralized with 6N HCl, washed with brine, dried over $MgSO_4$ filtered and the solvent evaporated under vacuum. The residue was swished in ether. This hydroxyketone (325mg) was then reacted as in example 1, Step 4 using phenylthioacetic acid (200mg)to give an intermediate (300mg) which was stirred in dichloromethane (2mL) and trifluoroacetic acid (8mL) for 18h. The solvents were then evaporated under vacuum and the residue was recrystallized from ethanol to afford the title compound.
^1H NMR (CD_3COCD_3) δ 1.65-2.20 (8H, m), 6.68 (2H, br s), 7.25 (5H, m), 7.55 (2H, d), 7.95 (2H, d).

EXAMPLE 23

3-(4-Fluorobenzyl)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Using a procedure similar to the one for example 16 but using 3-(4-fluorophenyl)propionyl chloride the title compound was obtained.
^1H NMR (CD_3COCD_3) δ 1.50 (6H, s), 3.15 (3H, s), 4.45 (2H, s), 7.05-7.15 (2H, m), 7.50-7.60 (2H, d), 7.85-7.95 (2H, m), 7.95-8.05 (2H, d).

EXAMPLE 24

3-(3,4-Difluorophenoxy)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)-phenyl)-5H-furan-2-one

Step 1: 2-Bromo-1-(4-(methylsulfonyl)phenyl)propan-1-one

Following a procedure similar to the one used in example 1, Step 1 but using propionyl chloride, 1-(4-(methylsulfonyl)phenyl)propan-1-one was obtained. A solution of this compund (163.4g) in chloroform (2.2L) was then cooled to 0°C and treated with bromine (40mL in 200mL $CHCl_3$) and concentrated HBr (10mL). The reaction mixture was washed with water, saturatd sodium bicarbonate and brine, dried over sodium sulfate, filtered and the solvent evaporated under vacuum. The residue was swished in ethyl acetate: hexane 1:1 to give the title compound (191g).

Step 2: 5-Hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenylthio-5H-furan-2-one

To a mixture of 2-bromo-1-(4-(methylsulfonyl)phenyl) propan-1-one (6.0g, 20.6mmol) and thiophenoxyacetic acid (3.8g, 22.6mmol) in acetonitrile (60mL) was added triethylamine (4.0mL, 28.8mmol). The mixture was stirred at r.t. for 3h. T.L.C. showed no bromoketone remaining and DBU (4.0mL) was added. The mixture was stirred at r.t. for 1h., then air was bubbled through the mixture for another hour. After dilution with water, the mixture was extracted with EtOAc. The EtOAc extract was washed with 1N aquous HCl, brine, dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. The residue was swished in Et_2O to give the title compound (6.0g) as a pale yellow powder.

^1H NMR (CD_3COCD_3) δ 1.68 (3H, s), 3.16 (3H, s), 6.86 (1H, s), 7.35 (5H, m), 7.78 (2H, d), 7.98 (2H, d).

Step 3: 5-Methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-phenylthio-5H-furan-2-one

The alcohol (2.5g, 6.6mmol) from the previous step was dissolved in methanol (100mL), THF (20mL) and concentrated HCl (5mL) and heated at 70°C for 24 h. After cooling to 0°C the precipitate formed was filtered, washed with methanol and dried under vacuum to give the title compound (2.0g) as a yellow solid.

^{1}H NMR (CD_3COCD_3) δ 1.65 (3H, s), 3.15 (3H, s), 3.40 (3H, s), 7.18-7.40 (5H, m), 7.88 (2H, d), 7.98 (2H, d).

Step 4: 3-(3,4-Difluorophenoxy)-5-methoxy-5-methyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

To a solution of the compound obtained in the previous step (2.0g, 5.1mmol) in dichloromethane (100mL) at r.t. was added mCPBA (4.0g, Aldrich 57-86%, ~16mmol). The mixture was stirred at r.t. for 3h and more mCPBA (2.0g) was added. After stirring for another hour the mixture was washed with 1N NaOH, brine, dried and concentrated under vacuum to yield a disulfone as a white foam (2.0g). To a solution of 3,4-difluorophenol (2.0g, 14.9mmol) in DMF was added 10N NaOH (1mL, 10mmol). After 30min. a solution of the above disulfone (2.0g, 4.7mmol) in DMF was added. The mixture was heated at 80-85°C for 1.5h. After cooling the mixture was diluted with water, extracted with EtOAc, the organic extracts were washed with 1N NaOH, 1N HCl, brine, dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. Purification by silica gel chromatography afforded the title compound as a white solid (600mg).

^{1}H NMR (CD_3COCD_3) δ 1.86 (3H, s), 3.16 (3H, s), 3.40 (3H, s), 6.95-7.40 (3H, m), 8.08 (2H, d), 8.16 (2H, d).

EXAMPLE 25

3-(5-Chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

To a mixture of 2-chloroacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (1.0g, 3.13 mmol, prepared similarly to the compound of example 5, Step 1) and 5-chloro-2-pyridinol (0.41g, 3.16 mmol) in CH_3CN (20 mL) was added DBU (1.5 mL, 10.0 mmol) at r.t.. The mixture was stirred for 1h, then heated at 65-70°C for 3h. The volatile solvents were removed in vacuo. The residue was chromatographed over silica gel and eluted with hexane:EtOAc (1:1) to

yield a colorless oily residue which was swished in Et_2O to provide the title compound as a white powder (230mg).
^1H NMR (CD_3COCD_3) δ 1.80 (6H, s), 3.20 (3H, s), 7.18 (1H, d), 7.94 (3H, m), 8.06 (2H, d), 8.19 (1H, d).

EXAMPLE 26

3-(2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 25, the title compound was prepared from 2-hydroxypyridine.
^1H NMR (CD_3COCD_3) δ 1.78 (6H, s), 3.15 (3H, s), 7.00-7.20 (2H, m), 7.80-8.20 (6H, m).

EXAMPLE 27

3-(6-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 25, the title compound was prepared from 2-hydroxy-6-methylpyridine.
^1H NMR (CD_3COCD_3) δ 1.75 (6H, s), 3.14 (3H, s), 6.85 (1H, d), 7.00 (1H, d), 7.70 (1H, t), 7.90 (2H, d), 8.00 (2H, d).

EXAMPLE 28

3-(3-Isoquinolinoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for example 25, the title compound was prepared from 3-hydroxyisoquinoline.
^1H NMR (CD_3COCD_3) δ 1.80 (6H, s), 3.14 (3H, s), 7.40-8.10 (9H, m), 9.00 (1H, s).

EXAMPLE 29

3-(4-(Methylsulfonyl)phenyl)-2-phenoxycyclopent-2-enone

Step 1: 1-(4-(Methylthio)phenyl)-5-phenoxypenta-1,4-dione

To a mixture containing 1-phenoxybut-3-en-2-one (1.0g) (A.G. Schultz, R.D. Lucci, W.Y. Fu, M.H. Berger, J. Erhardt and W.K. Hagmann, J. Amer. Chem. Soc. **100**, 2150, (1978)), 4-(methylthio)benzaldehyde (0.62g) and triethylamine (0.343mL) in 1,4-dioxane (20 mL) was added 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (110mg). After stirring 4h. at 100°C the reaction mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. The residue was purified by silica gel chromatography (20% EtOAc/Hexane) to afford 140mg of the title compound as an oil.

Step 2: 3-(4-(Methylthio)phenyl)-2-phenoxycyclopent-2-enone

To the diketone of Step 1 (120mg) in methanol (80mL) was added DBU (0.1mL). The resulting mixture was heated at 60°C for18 h. The methanol was then evaporated and to the crude mixture was added saturated aqueous ammonium chloride, the mixture was then extracted with EtOAc, the organic layer was dried over $MgSO_4$, filtered, and the solvent evaporated under vacuum. The residue was purified by silica gel chromatography (20% EtOAc/hexane) to afford the title compound.

Step 3: (4-(Methylsulfonyl)phenyl)-2-phenoxycyclopent-2-enone

To the compound obtained in Step 2 (60mg) in dichloromethane (4.5mL) and methanol (2.4mL) was added Oxone® (450mg) in water (1mL) and the reaction mixture was stirred for 1 h.Water was added to the mixture which was then extracted with dichloromethane, the organic layers were combined and dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. Purification by silica gel chromatograohy afforded the title compound.

^{1}H NMR (CD_3COCD_3) δ 2.65 (2H, t), 3.15 (3H, s), 3.20 (2H, t), 7.05-7.35 (5H, m), 8.10 (4H, m).

EXAMPLE 30

2-(3,4-difluorophenoxy)-3-(4-methylsulfonylphenyl)-cyclopent-2-enone

Step 1: 3,4-Difluorophenoxymethyl vinyl ketone

To a suspension of 3,4-difluorophenoxy acetic acid (5.00 g, 25.7 mmol) lithium salt in DME (20 mL) was added to a 1M THF solution of vinyl magnesium bromide (38 mmol). After a period of 18h, the resulting clear solution was poured over 1N HCl (67 mL). The aqueous phase was then extracted with Et_2O. The ethereal phase was washed with H_2O, 1M K_2CO_3 then H_2O. After drying over $MgSO_4$ and evaporation an orange oil was obtained and used as such for the next step.

Step 2: 2-(3,4-difluorophenoxy)-3-(4-methylsulfonylphenyl)-cyclopent-2-enone

Following the procedure described in Example 29 but using the compound obtained in the previous step the title compound was obtained.

^{1}H NMR (CD_3COCD_3) δ 2.60 (2H, t), 3.15 (3H, s), 3.20 (2H, t), 6.90 (1H, m), 7.15 (1H, m), 7.25 (1H, Q), 8.10 (4H, 2d).

EXAMPLE 32

3-(5-Benzothiophenyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 5-hydroxybenzothiophene.

M.P.: 150-152°C ^{1}H NMR (CD_3COCD_3) δ 1.78 (6H, s), 3.08 (3H, s), 7.17 (1H, dd), 7.32 (1H, d), 7.56 (1H, d), 7.68 (1H, d), 7.92 - 7.99 (5H, m).

EXAMPLE 37

5,5-dimethyl-4-(4-methylsulfonyl-phenyl)-3-(pyridin-4-yloxy)-5H-furan-2-one

To a R.T. solution of 2-chloroacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (318 mg, 1 mmol) in DMF (5 mL) was added 4-pyridone (380 mg, 4.0 mmol) followed by DBU (623 mg, 4.1 mmol) and the mixture was slowly warmed up to R.T. for 16 hrs and then to 60-70 °C for 1-2 hours. The mixture was cooled to R.T. and poured on icy dilute NH_4Cl and EtOAc; the organic layer was separated and the aqueous further extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and the solvents were removed *in vacuo*. The residue was purified on silica gel chromatography (1/1, Acetone/toluene) to provide the title compound.

^1H NMR (CD_3COCD_3)δ 1.8(6H,s), 3.15(3H,s), 7.05-7.15(2H,m), 7.9-8.1(4H,AB), 8.4-8.5(2H,m).

EXAMPLE 38

5,5-dimethyl-4-(4-methylsulfonyl-phenyl)-3-(pyridin-3-yloxy)-5H-furan-2-one

To a R.T. solution of 2-chloroacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (318 mg, 1 mmol) in DMF (5 mL) was added 3-hydroxypyridine (95 mg, 1 mmol) followed by DBU (623 mg, 4.1 mmol) and the mixture was slowly warmed up to R.T. for 16 hrs and then to 60-70 °C for 1-2 hours. The mixture was cooled to R.T. and poured on icy dilute NH_4Cl and EtOAc; the organic layer was separated and the aqueous further extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and the solvents were removed *in vacuo*. The residue was purified on silica gel chromatography (1/1, Acetone/toluene) to provide the title compound.

Analysis calculated for $C_{18}H_{17}NO_5S$: C, 60.16; H, 4.77; N, 3.90.
Found: C, 60.01; H, 4.81; N, 3.90.

EXAMPLE 39

3-(2-Methyl-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 5-hydroxy-2-methyl pyridine M.P.: 168 - 169°C.

^{1}H NMR (CD_3COCD_3) δ 1.77 (6H, s), 2.41 (3H, s), 3.15 (3H, s), 7.14 (1H, d), 7.37 (1H, dd), 7.93 (2H, d), 8.03 (2H, d), 8.25 (1H, d).

EXAMPLE 44

3(2-Fluoro-4-trifluoromethyl)phenoxy-4-(4-methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one

Following the procedure for Example 25, the title compound was prepared from 2-fluoro-4-trifluoromethylphenol; m.p.: 192-194. ^{1}H NMR (CD_3COCD_3) d 1.78 (6H, s), 3.16 (3H, s), 7.49 (2H, m), 7.64 (1H, d, J = 11.6 Hz), 7.95 (2H, d, J = 8.3 Hz), 8.05 (2H, d, J = 8.5 Hz). Analysis calculated for $C_{20}H_{16}F_4O_5S$: C, 54.06; H, 3.63; Found: C, 54.09, H, 3.72.

EXAMPLE 45

3-(5-Chloro-2-pyridylthio)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 5-chloro-2-mercaptopyridine.

^{1}H NMR(CD_3COCD_3) δ 1.70(6H, s), 3.20(3H, s), 7.38(1H, d), 7.72(3H, m), 8.06(2H, d), 8.42(1H, m).

EXAMPLE 46

2-(3,5-Difluorophenoxy)-3-(4-methylsulfonylphenyl)-cyclopent-2-enone

Using similar protocol described for Example 29 but using 1-(3,5-difluorophenoxy)but-3-en-2-one the title compound was obtained.

^{1}H NMR (CD_3COCD_3) δ 2.60 (2H, t), 3.15 (3H, s), 3.20 (2H, t), 6.60 to 6.85 (3H, m), 8.10 (4H, 2d).

EXAMPLE 47

3-(2-Pyrimidinoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxypyrimidine hydrochloride.

^{1}H NMR(CD_3COCD_3) δ 1.78(6H, s), 3.18(3H, s), 7.34(1H, t), 7.40(2H, d), 8.06(2H, d), 8.68(2H, d).

EXAMPLE 48

3-(3-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 2-Hydroxy-3-methylpyridine

To 10% aqueous H_2SO_4(90mL) at 0^{O}C was added 2-amino-3-methylpyridine (6.0g, 56mmol). The mixture was stirred at 0^{O}C for 30mins and a solution of 4N aqueous $NaNO_2$ (13mL) was added dropwise over a period of 15 min. The mixture was further stirred and warmed to rt over 1h. The pH was then adjusted to 6-7 by the addition of 10N aqueous NaOH. The whole mixture was then extracted with $CHCl_3$, washed with H_2O, dried (anhydrous $MgSO_4$) and concentrated *in vacuo*.

The crude material was swished with Et_2O to give the title compound (2.5g, 42%) as a white solid.

^1H NMR(CD_3COCD_3) δ 2.02(3H, s), 6.10(1H, m), 7.30(2H, m).

Step 2: 3-(3-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-3-methylpyridine.

^1H NMR(CD_3COCD_3) δ 1.78(6H, s), 2.30(3H, s), 3.14(3H, s), 7.05(1H, m), 7.65(1H, m), 7.95(3H, m), 8.02(2H, d).

EXAMPLE 49

3-(3-Chloro-5-pyridiloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 2-chloro-5-hydroxypyridine. M.P.: 176 - 177°C.

^1H NMR (CD_3COCD_3) δ 1.79 (6H, s), 3.16 (3H, s), 7.70 (1H, m), 7.96 (2H, d), 8.05 (2H, d), 8.33 (1H, d), 8.40 (1H, d).

EXAMPLE 51

3-(3-(1,2,5-Thiadiazolyl)oxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one

Following the procedure for example 25, the title compound was prepared from 3-hydroxy-1,2,5-thiadiazol; m.p.: 127-129.

^1H NMR (CD_3COCD_3) δ 1.78 (6H, s), 3.16 (3H, s), 7.92 (2H, d, J = 8.6 Hz), 8.06 (2H, d, J = 8.6 Hz), 8.49 (1H, s).

Analysis calculated for $C_{15}H_{14}N_2O_5S_2$: C, 49.17; H, 3.85; N, 7.65; Found: C, 49.01, H, 3.84; N, 7.37.

EXAMPLE 52

3-(5-Isoquinolinoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 5-hydroxyisoquinoline.

^{1}H NMR(CD_3COCD_3) d 1.80(6H, s), 3.10(3H, s), 7.38(1H, d), 7.55(1H, t), 7.85(1H, d), 7.95(4H, m), 8.04(1H, d), 8.58(1H, d), 9.30(1H, s).

EXAMPLE 53

3-(6-Amino-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-6-aminopyridine.

M.P.: 165-166°C. ^{1}H NMR (CD_3COCD_3) δ 1.74 (6H, s), 3.14 (3H, s), 5.52 (2H, s, br), 6.17 (1H, d), 6.24 (1H, d), 7.41 (1H, t), 7.90 (2H, d), 8.02 (2H, d).

EXAMPLE 54

3-(3-Chloro-4-fluoro)phenoxy-4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one

Following the procedure for Example 25, the title compound was prepared from 3-chloro-4-fluorophenol; m.p.: 130-132°C.

^{1}H NMR (CD_3COCD_3) δ 1.76 (6H, s), 3.14 (3H, s), 7.10 (1H, m), 7.24 (1H, t, J = 9Hz), 7.30 (1H, m), 7.92 (2H, d, J = 8.5 Hz), 8.03 (2H, d, J = 8.5 Hz).

EXAMPLE 55

3-(6-Quinolinoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 6-hydroxyquinoline. M.P.: 171-172°C.

^{1}H NMR (CD_3COCD_3) δ 1.82 (6H, s), 3.08 (3H, s), 7.46 (1H, m), 7.53 - 7.60 (3H, m), 7.95 - 8.01 (5H, m), 8.23 (1H, m), 8.80 (1H, m).

EXAMPLE 56

3-(5-Nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-5-nitropyridine.

^{1}H NMR(CD_3COCD_3) δ 1.80(6H, s), 3.18(3H, s), 7.38(1H, d), 7.92(2H, d), 8.05(2H, d), 8.66(1H, m), 9.05(1H, m).

EXAMPLE 57

3-(2-Thiazolylthio)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 2-mercaptothiazole. M.P.: 174-176°C.

^{1}H NMR (CD_3COCD_3) δ 1.67 (6H, s), 3.19 (3H, s), 7.59 (1H, d), 7.68 (1H, d), 7.74 (2H, d), 8.07 (2H, d).

EXAMPLE 58

3-(3-Fluoro-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 5-fluoro-2-hydroxypyridine M.P.: 157 - 159°C.

^{1}H NMR (CD_3COCD_3) δ 1.76 (6H, s), 3.16 (3H, s), 7.16 (1H, m), 7.74 (1H, m), 7.92 (2H, d), 8.03 (2H, d), 8.07 (1H, m).

EXAMPLE 109A

5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one

Step 1: 5,5-Dimethyl-3-hydroxy-4-(4-methylsulfonylphenyl)-

To a 0°C solution of the alcohol of Example 1, Step 3 (29.5 g, 122 mmol) in CH_3CN (350 mL) were added pyridine (25 mL) and acetoxyacetyl chloride (25 g, 183 mmol). After a period of 7h at r.t., DBU (31 mL) was added to the reaction mixture. After a period of 1h at 80°C, a second portion of DBU (35 mL) was added. The reaction mixture was kept at 80°C for 18h. The reaction mixture was allowed to cool to r.t. The mixture was poured onto ice-water (2.5L) containing 100 mL of concentrated HCl. The brown solid was collected and dissolved in hot acetonitrile and was filtered through a plug of silica. The solvent was evaporated and the resultant solid was swished in EtOAc to give the title compound (21.2g, 62%).

Step 2: 5,5-Dimethyl-4-(4-methylsulfonyl)phenyl)-3-(-2-propoxy)-5H-furan-2-one

To a suspension of the alcohol of Step 1 (18.16 g, 64.4 mmol) in benzene (350 mL) were added an excess of 2-iodopropane

(19.3 mL) and Ag_2CO_3 (53.3 g, 1.06 mmol). After stirring for 18h , the reaction mixture was filtered and the filtrate was washed with hot EtOAc. After evaporation, the crude compound was purified by flash chromatography (35% to 40% EtOAc/hexane, followed by addition of 5% CH_2Cl_2) to provide 19 g of the title compound.

^1H NMR (CD_3COCD_3) δ 1.25 (6H, d), 1.70 (6H, s), 3.20(3H,s), 5.20(1H,septet), 8.05 (4H, s).

EXAMPLE 109b

5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one

Step 1: 5,5-Dimethyl-3-hydroxy-4-(4-methylsulfonylphenyl)-5H-furan-2-one

To a 0°C solution of the alcohol of Example 1, Step 3 (14.0 g, 57.8 mmol) in CH_3CN (180 mL) were added pyridine (10.0 mL) and acetoxyacetyl chloride (12.7 g, 93.0 mmol) after a period of 7h at r.t., DBU (15.0 mL) was added to the reaction mixture. After a period of 1h at 80°C, a second portion of DBU (20.0 mL) was added. The reaction mixture was kept at 80°C for 18h. The reaction mixture allowed to cool to r.t. The mixture was diluted with EtOAc (500 mL) and H_20 (500 mL) and acidified with 6NHCl. After the addition of brine (100 mL), the aqueous phase was extracted 2 times with EtOAc. The organic phase was evaporated to provide a brown residue. To the solid was added a 2:1 mixture of CH_2Cl_2 - toluene (150 mL). The solid was filtered and washed with CH_2Cl_2 - toluene to provide 7.0 g of the title compound.

Step 2: 5,5-Dimethyl-4-(4-methylsulfonyl)phenyl)-3-(-2-propoxy)-5H-furan-2-one

To a suspension of the alcohol of Step 1 (100 mg, 0.354 mmol) in benzene (5.0 mL) were added an excess of 2-iodopropane (105 mL) and Ag_2CO_3 (294 mg, 1.06 mmol). After a period of 18h at 45°C, the reaction mixture was filtered over celite and washed with CH_2CL_2. After evaporation, the crude compound was purified by flash

chromatography (35% to 40% EtOAc) to provide 70 mg of the title compound.

^{1}H NMR (CD_3COCD_3) δ 1.25 (6H, d), 1.70 (6H, s), 3.20 (3H, s), 5.20 (1H, Septet), 8.05 (4H, s).

Alternatively compound 109 may be prepared in the following manner:

Step A 1: 2-Methyl-1-(4-(thiomethyl)phenyl)propan-1-one

A 500 mL flask was charged under N_2 with 34.5g (259 mMol) of $AlCl_3$ and 100 mL of ODCB. The vigorously stirred slurry was cooled to 8°C and isobutyryl chloride (28.6 mL, 261 mMol) was added over 30 min., keeping the temperature at 10-15°C.

The addition of isobutyryl chloride was slightly exothermic. The $AlCl_3$/isobutyryl chloride complex was aged at 7°C for 30 min. Efficient cooling was applied and thioanisole (31.2g) was added to the reaction mixture over 120 min., maintaining an internal temperature of 8-13°C.

The addition of thioanisole was very exothermic. After the addition of about half of thioanisole a heavy yellow precipitate formed. The precipitation was accompanied by an exotherm. Gaseous HCl is formed in the reaction, so that the effluent gas stream should be scrubbed with aqueous NaOH before release into the atmosphere.

The reaction was warmed to 16°C over 1h.

The reaction mixture was a thick yellow slurry at this point. HPLC analysis of a quenched (EtOAc/H_2O) aliquot indicated completion of reaction.

The reaction mixture was cooled to 10°C and 160 mL of 5% aqueous HCl were added over 45 min.

The addition was extremely exothermic and especially the initial addition required careful temperature monitoring.

The biphasic mixture was vigorously stirred for 60 min. The lower organic phase was removed.

A quantitative assay of the organic phase indicated a 98% yield.

Step A 2: 2-Bromo-2-methyl-1-(4-(thiomethyl)phenyl)propan-1-one

A 500 mL flask was charged with the solution of the compound from step A 1 (246 mMol) . Approximately 10% of the bromine (1.3 mL, 26 mMol) were added and the reaction mixture was stirred until the red color had dissipated after 45 min. The remainder of the Br_2 (12 mL) was added over 60 min.

The reaction was exothermic and the temperature rose to ca. 32°C.

Gaseous HBr was released from the reaction, thus the effluent gas stream was scrubbed with aqueous NaOH before release into the atmosphere.

The reaction mixture was aged for 2 h at 30°C when HPLC analysis indicated completion of the reaction

Addition of a slight excess of Br_2 leads to the partial oxidation of the sulfide to the sulfoxide .

The reaction was quenched by the addition of 160 mL H_2O and the resulting 182.0 mL of organic phase were used directly for the oxidation (next step) (95% assay yield).

Step A 3: 2-Bromo-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one

To a solution of the compound from the previous step in ODCB in a 500 mL reaction vessel with heating jacket, reflux condenser and bottom valve was added under N_2 a solution of Na_2WO_4 (0.45g, 1.4mMol) and Aliquat 336 (2.2g, 5.4 mMol) in 3.0 mL H_2O. The

heterogeneous reaction mixture was heated with vigorous stirring to 35°C and ca. 3.0 mL of H_2O_2 (30%) were added.

The oxidation was extremely exothermic. After an induction period of ca. 3 min. the temperature rose quickly to 50-65°C.

The remainder of the H_2O_2 (36 mL) was added over 1 h. At the end of the addition HPLC analysis indicated completion of the reaction.

The reaction mixture was heated to 80°C, the lower organic phase was removed and cooled to 6°C over 1 h.

The product precipitated at ca. 50°C without seeding.

The slurry was filtered and washed with 25.0 mL of ODCB and 30.0 mL of hexane and three times with 20.0 mL of 60°C H_2O. After drying 37.8 g of the title compound (97% yield, ca. 91% overall yield from thioanisole) were obtained as a white powder.

Step A 4: Isopropoxyacetic acid

A 500 mL vessel fitted with a mechanical stirrer, thermocouple probe, and nitrogen inlet is charged with 200 mL of IPA (K.F. 220 µg/mL) and sodium hydroxide (6.0 g, 0.145 mol). The mixture was heated at reflux until the solid sodium hydroxide dissolved.

A homogeneous solution is obtained after reflux for 3 h.

The solution was cooled at ~ 70 °C and toluene (15.0 mL) was added. It was distilled until ~100 mL of distillate was collected. A mixture of IPA/toluene (85:15, 100 mL) was added and ~ 0.1L of liquid was distilled off (repeated 3 x). At the end of distillation (~0.4 L of distillate collected), the solution was diluted with IPA to a volume of ~ 300 mL.

The distillate is assayed to determine the amount of water removed. If the water removed is < 75% of the theoretical amount (K.F. of IPA + that in NaOH + 1 equiv generated), the distillation should be continued. The solution was then cooled at 60-70 °C and sodium

chloroacetate (15.9 g, 0.134 mol) was added in portions over 5 min. No exotherm is observed during the addition.

The mixture was heated at reflux for 3 h and a sample of the slurry was taken for assay.

The reaction is followed by ^{1}HNMR. An aliquot (~0.2 mL) of the mixture is taken and evaporated to dryness. The residue is dissolved in D_2O for ^{1}HNMR measurement. The reaction is considered completed when the starting material is < 3 % *vs*. product.

The reaction was quenched by addition of 60.0 mL of water and concentrated under reduced pressure (150-200 mBar, 50-60 °C) until ~250 mL of distillate was collected. More water was added (40.0 mL) and the solution was distilled at normal pressure until the batch temperature reached ~103 °C (~ 100mL of solution left, ~300 mL of solvent removed). The solution was cooled at 10-20 °C and neutralized by addition of conc. hydrochloric acid (12.5 mL, 0.15 mol).

External cooling may be needed during the addition of acid. The final pH should be < 2.3, preferably ~2.

t-Butyl methyl ether (80.0 mL) was added. The aqueous solution was saturated with sodium chloride (~ 9.0 g) and the two-phase mixture was agitated for 0.5 h at 10-15 °C. The layers were separated and the aqueous layer was back extracted with 2 x 60.0 mL of t-butyl methyl ether. The organic layers were combined and washed with 2 x 10.0 mL of saturated aqueous sodium chloride.

The pH of the 2nd brine wash should be > 2.5.

The organic solution was dried over 4A molecular sieves (10.0 g) for 14 h and filtered. The sieves were washed with 3 x 15.0 mL of t-butyl methyl ether. t-Butyl methyl ether was removed under reduced pressure (~200 mBar, 45-50 °C). Isopropoxyacetic acid was obtained as a slightly yellow liquid.

Yield: 11.8 g, 75 % yield.

Step A 5: 2-(isopropoxy)acetic acid 2-methyl-1-(4-methylsulfonyl)phenyl)propan-1-one-2-yl ester

A 100 mL flask was sequentially charged with dry ethanol (45.0 mL, K.F. < 100 μg/mL), isopropoxyacetic acid (2.32 g) , diisopropylethylamine (4.85 mL) and the bromosulfone (step A 3)(5.0 g). The mixture is heated to reflux until the bromosulfone is not detected (HPLC, reaction time 12-14 hours).

The reaction is considered complete when the bromosulfone is < 0.05 A% vs. product.

After the reaction was complete, the solution was allowed to cool and seeded at 42°C. Crystallization initiated immediately and the mixture was cooled to 1° C and aged 1 hr. The product ester is filtered and washed with ethanol (0°C 5.0 mL wash). After drying in a vacuum oven, the white crystalline title compound was used as is in the next step. Yield: 4.15 g.

Step A 6: 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(2-propoxy)-5H-furan-2-one

A 1L flask was sequentially charged with dry acetonitrile (320 mL, K.F. < 100 μg/mL), isopropyl trifluoroacetate (30.1 g, 0.193 mol), and DBU (36.70 g, 0.24 mol). The solution was stirred at ~20 °C for 15 min and the ester from Step A5 (55.0 g, 0.161 mol) was added. The solution was heated at reflux under nitrogen and the progress of the reaction was followed by HPLC.

The reaction is considered complete when the intermediate peaks are < 0.2 A% vs. product.

After the reaction was complete, the solution was cooled at ~40 °C and filtered (1 μ in-line capsule). The solution was then concentrated at 40-50 °C under reduced pressure until ~0.20 L of

distillate was collected. Water (350 mL) was added slowly at ~45 °C. After ~130 mL of water was added, the solution turned cloudy (40-45 °C) and ~0.02 g of crystalline title compound was added as the seed. The mixture was aged for 30 min and the remaining water was added. The mixture was aged at ~20 °C for 6 h then filtered. The cake was washed with 2 x 65 mL of 1:4 MeCN/water and 3 x 65 mL of water. The title product was air dried and dried *in vacuo* (35 °C, 200 mBar).

Yield: ~48.0 g, 92%.

EXAMPLE 110

3-(3-Trifluoromethyl)phenoxy-4-(4-methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 3-trifluoromethylphenol.
^{1}H NMR (CD_3COCD_3) δ 1.79 (6H, s), 3.14 (3H, s), 7.41 (3H, m), 7.55 (1H, m), 7.95 (2H, dd, J = 2, 6.6 Hz), 8.03 (2H, dd, J = 2, 6.7 Hz).
Analysis calculated for $C_{20}H_{17}F_3O_5S$: C, 56.34; H, 4.02; Found: C, 56.21, H, 4.01.

EXAMPLE 111

5,5-Dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(piperidine-1-carbonyl)-5-H-furan-2-one.

Step 1: 5,5-Dimethyl-4-(4-(methylsulfonyl)phenyl)-2-oxo-2,5-dihydrofuran-3-carboxylic acid ethyl ester

A mixture of 2-hydroxy-2-methyl-1-(4-(methylsulfonyl) phenyl)propan-1-one (2.87 g, 11.8 mmol), ethyl hydrogen malonate (2.02 g, 15.3 mmol), CMC (6.51 g, 15.4 mmol) and DMAP (0.35 g, 2.8 mmol) was dissolved in 100 mL of CH_2Cl_2. The mixture was stirred for 14h at room temperature, then DBU (4 mL, 27 mmol) was added, stirred 1h, then partitioned between CH_2Cl_2 and 1M HCl. The organic layer was washed with brine, filtered through cotton

and evaporated. Purification by flash chromatography (90% ether/Hex) provided 2.50 g of the title compound.
^{1}H NMR (CD_3COCD_3) δ 8.09 (2H, m), 7.68 (2H, m), 4.05 (2H, q), 3.16 (3H, s), 1.58 (6H, s), 0.96 (3H, t).

Step 2: 5,5-Dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(piperidine-1-carbonyl)-5H-furan-2-one

To a room temperature solution of piperidine (284 mg, 3.33 mmol) in CH_2Cl_2 (5mL) was added trimethylaluminum (2M in hexane, 1.7 mL, 3.4 mmol). After 15 min, the product from Step 1 (310 mg, 0.92 mmol) was added in one portion and the mixture was heated to reflux for 20h. The resulting solution was cooled and poured into 1M HCl (gas evolution). The organic layer was washed with brine, filtered through cotton and evaporated. Purification by flash chromatography (80% EtOAc/Hex) provided 175 mg of the title compound.
^{1}H NMR (CD_3COCD_3) δ 8.08 (2H, m), 7.80 (2H, m), 3.49 (2H, m), 3.35 (2H, m), 3.17 (3H, s), 1.65 (6H, s), 1.55 (2H, m), 1.40 (4H, m).

EXAMPLE 112

5,5-Dimethyl-3-(2-butoxy)-4-(4-methylsulfonylphenyl)-5H-furan-2-one

Step 1: 5,5-Dimethyl-3-(2-butoxy)-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one

To a suspension of the alcohol of Example 109, Step 1 (300 mg, 1.06 mmol) in benzene (20.0 mL) were added 2-iodobutane (300 μL) and Ag_2CO_3 (400 mg, 3.27 mmol). After a period of 4h at 45°C, the reaction mixture was filtered over celite and washed with CH_2Cl_2. After evaporation, the crude product was purified by flash chromatography (35% EtOAc in Hexane) to give 150 mg of the title compound as a white solid.
^{1}H NMR (CD_3COCD_3) δ 0.09 (3H, t), 1.20 (3H, d), 1.65 (6H, s), 3.20 (3H, s), 5.00 (1H, m), 8.00 (4H, s).

EXAMPLE 113

5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(3-pentoxy)-5H-furan-2-one

Step 1: Pentyl-3-oxyacetic acid

To a solution of 3-pentanol (17.6 g, 200 mmol) in benzene (200 mL) was added NaH (6.0 g, 400 mmol). After 1h at r.t., chloroacetic acid sodium salt (25.6 g, 200 mmol) was added to the previous mixture. After a period of 2hr. at reflux, the reaction mixture was pourred in H_2O and acidified with HCl. The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered over silicic acid (30% EOAc in Hexane). After evaporation of the solvents the title compound was purified by distillation (5.0 g).

Step 2: Pentyl-3-oxyacetic acid 2-methyl-1-(4-methylsulfonylphenyl)propan-1-one-yl ester

The title compound was obtained using similar protocol as described for Example 1 Step 3.

Step 3: 5,5-Dimethyl-4-(4-methylsulfonylphenyl)-3-(3-pentylxy)-5H-furan-2-one.

To a solution of the ester of Step 2 (500 mg, 1.35 mmol) in DMF (2.5 mL) was added NaH (50 mg, 1.6 mmol). The reaction mixture was heated gently to give an orange mixture. After standard extractive workup procedure (EtOAc), the crude mixture was purified by flash chromatography (35% EtOAc in hexane to afford 115 mg of the title compound by filtration in Et_2O/hexane.

^1H NMR (CD_3COCD_3) δ 0.85 (6H, t), 1.60 (4H, m), 1.65 (6H, s), 3.20 (3H, s), 4.90 (1H, quintet), 8.05 (4H, s).

EXAMPLE 115

2-(5-Chloro-2-pyridinoxy)-3-(4-methylsulfonylphenyl)-cyclopent-2-enone

Using similar protocol described for Example 29 but using 1-(5-chloropyridyl-2-oxy)but-3-en-2-one the title compound was obtained.

^{1}H NMR (CD_3COCD_3) δ 2.50 (2H, t), 2.80 (3H, s), 3.10 (2H, t), 7.10 (1H, d), 7.30 (2H, d), 7.80 (2H, d), 7.85 (1H, dd), 8.05 (1H, d).

EXAMPLE 116

3-(4-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-4-methylpyridine.

^{1}H NMR(CD_3COCD_3) δ 1.76(6H, s), 2.36(3H, s), 3.15(3H, s), 6.90(1H, s), 6.98(1H, d), 7.89(2H, d), 7.98(1H, d), 8.02(2H, d).

EXAMPLE 117

(5R)-3-(3,4-Difluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 2-(S)-t-butyl-5-(R)-ethyl-4-hydroxy-5-methyl-4-(4-(methylthio)phenyl)-1,3-dioxolan-4-one

To a solution of 4-bromothioanisole (27.3 g, 134 mmol) in 300 ml of anhydrous THF at -72°C was added 2.5 M n-BuLi in hexanes (54 ml, 135 mmol) at such a rate as to maintain the internal temperature below -55°C and the mixture was stirred at -72°C for an hour. A solution of 2-(S)-t-butyl-5-(R)-ethyl-5-methyl-1,3-dioxolan-4-one (16.8 g, 90 mmol, *Tetrahedron*, **1984**, *40*, 1313) in 50 ml of THF was added dropwise and the mixture was stirred at -72°C for 15 minutes. Acetic

acid (13 ml) was then added slowly and the mixture stirred for another 10 min. at -72°C. The reaction was quenched with 25% aq. NH_4OAc at -72°C and allowed to warm up to r.t. The title product was extracted in i-PrOAc, dried over Na_2SO_4 and purified by flash chromatography on silica with EtOAc/hexane 2.5 and 5% to yield 22.4 g (80%) of a white solid.

^1H NMR ($CDCl_3$, mixture of 2 diastereoisomers 1.8:1) d 0.58, 1.52, 1.68 and 2.05 (2H, 4m), 0.70 and 1.36 (3H, 2s), 0.73 and 0.98 (3H, 2T), 1.00 (9H, 2s), 2.47 (3H, 2s), 2.47 and 2.57 (1H, 2s,)H), 4.80 and 5.00 (1H, 2s), 7.20 (2H, 2d), 7.45 (2H, 2d).

Step 2: 2-(R)-hydroxy-2-methyl-1-(4-(methylthio)phenyl)-1-butanone

A mixture of the product of step 1 (32.0 g, 103 mmol), p-toluenesulfonic acid (900 mg) and 35 ml of water was heated to reflux for an hour. The title product was extracted in 200 mL of EtOAc and the solution used as such in the next step.

Step 3: 2-(R)-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)-1-butanone-1-one

To the product of Step 2 in 200 ml of EtOAc in an ice bath (to maintain the temperature of the reaction below 25°C) was added 100 ml of t-BuOH, 2.3 g of Aliquat 336® and a solution of 73.1 g of Oxone® (238 mmol $KHSO_5$) in 450 ml of water and the mixture was stirred at r.t. overnight. It was then neutralized with 10N NaOH. The title product was extracted in i-PrOAc, dried over Na_2SO_4, and purified by flash chromatography on silica with EtOAc/toluene 20 & 40% to yield 23.8 g of a colorless oil. NMR experiments with the chiral shift reagent Eu (hfc)3 indicated an enantiomeric excess superior than 94%. $[\alpha]_D^{25}$ = -11.2° (c = 0.8, $CHCl_3$) .

^1H NMR ($CDCl_3$) δ 0.87 (3H, t), 1.57 (3H, s), 1.93 (2H, m), 3.07 (3H, s), 3.53 (1H, s), 8.00 (2H, d), 8.13 (2H, d).

Step 4: (5R)-3-(3,4-Difluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 1, step 4, the title compound was prepared from 3,4-difluorophenoxyacetic acid and (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-butan-1-one.

$[\alpha]_D = +9.4^O$(c 0.9, acetone).

^{1}H NMR(CD_3COCD_3) δ 0.95(3H, t), 1.80(3H, s), 2.12(2H, q), 3.18(3H, s), 6.95(1H, m), 7.14(1H, m), 7.30(1H, m), 7.95(2H, d), 8.06(2H, d).

EXAMPLE 118

(5R)-3-(4-Chlorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 117, the title compound was prepared from 4-chlorophenoxyacetic acid and (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-butan-1-one.

^{1}H NMR(CD_3COCD_3) δ 0.93(3H, t), 1.78(3H, s), 2.12(2H, q), 3.15(3H, s), 7.11(2H, d), 7.35(2H, d), 7.92(2H, d), 8.03(2H, d).

EXAMPLE 119

3-(2-Methyl-3-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 3-hydroxy-2-methylpyridine.

^{1}H NMR(CD_3COCD_3) δ 1.77(6H, s),2.48(3H, s), 3.14(3H, s), 7.08(1H, m), 7.33(1H, d), 7.93(2H, d), 8.02(2H, d), 8.16(1H, m).

EXAMPLE 120

3-(4-Methyl-5-nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)-phenyl-5H-furan-2-one

A mixture of 3-hydroxy-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one(1.5g, 5.3mmol, Example 109 step 1), 2-chloro-4-methyl-5-nitropyridine(1.0g, 5.8mmol) and powdered KOH(300mg, 5.4mmol) in DMF(20mL) was heated at 100°C for 12h. After cooling to r.t., the mixture was diluted with H_2O, extracted with EtOAc. The EtOAc extract was washed with brine, dried(anhydrous $MgSO_4$) and concentrated *in vacuo*. The residue was swished with EtOH to give the title compound as a pale yellow solid(1.7g, 77%).

^1H NMR (CD_3COCD_3) δ 1.80(6H, s), 2.68(3H, s), 3.16(3H, s), 7.20(1H, s), 7.90(2H, d), 8.05(2H, d), 8.85(1H, s).

EXAMPLE 121

3-(5-Chloro-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)-phenyl-5H-furan-2-one

Step 1: 3-(5-Amino-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

A mixture of 3-(4-methyl-5-nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one(1.4g, 3.3mmol), iron powder(1.5g, 27mmol) and NH_4Cl(150mg) in 67% aqueous EtOH(45mL) was refluxed for 1h. The hot mixture was filtered through celite. Volatile solvent was evaporated *in vacuo*. The residue was suspended in water, filtered and dried under vacuum to give the title compound as a brown powder(1.2g, 94%).

^1H NMR (CD_3COCD_3) δ 1.72(6H, s), 2.20(3H, s), 3.15(3H, s),4.42(2H, brs), 6.75(1H, s), 7.50(1H, s), 7.90(2H, d), 8.00(2H, d).

Step 2: 3-(5-Chloro-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

To a suspension of 3-(5-amino-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one(600mg, 1.6mmol) in 6M aqueous HCl(3mL) at 0°C was added dropwise a solution of 4M aqueous $NaNO_2$(450mL, 1.8mmol). The solution became clear and then precipitate formed. After stirring for 30min, the diazotization mixture was added to a solution of CuCl(300mg, 3.0mmol) in concentrated HCl(2mL) at 0°C, then heated to 70-80°C for 10min, cooled to r.t. and diluted with H_2O and dried under vacuum. Recrystallization from EtOH-Acetone yielded the title compound as a light yellow solid(360mg, 57%).

^1H NMR (CD_3COCD_3) δ 1.76(6H, s), 2.40(3H, s), 3.16(3H, s), 7.10(1H, s), 7.90(2H, d), 8.05(2H, d), 8.10(1H, s).

EXAMPLE 122

3-(5-Fluoro-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)-phenyl-5H-furan-2-one

To a suspension of 3-(5-amino-4-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one(650mg, 1.68mmol, Example 121 step 1) in 6M aqueous HCl(4mL) at 0^oC was added dropwise a solution of 4M aqueous $NaNO_2$(450mL, 1.8mmol). After stirring at 0^oC for 30min, 60% aqueous HPF_6(2mL) was added and the mixture was further stirred for 30min. The precipitate was collected, washed with H_2O and dried under vacuum to give 850mg of diazonium salt.

The diazonium salt was then heated with a propane torch until the compound started to decompose. The dark brown residue was dissolved in acetone and chromatographed over silica gel, eluted with hexanes:EtOAc(2:3) to provide the title compound as a pale yellow solid(100mg, 17%).

^{1}H NMR (CD_3COCD_3) δ 1.72(6H, s), 2.34(3H, s), 3.16(3H, s), 7.02(1H, m), 7.90(2H, d), 7.94(1H, s), 8.02(2H, d).

EXAMPLE 123

3-(3-Chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 3-(3-Nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

A mixture of 3-hydroxy-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one(1.5g, 5.3mmol), 2-chloro-3-nitropyridine(1.0g, 6.3mmol) and powdered KOH(320mg, 5.7mmol) in DMF(20mL) was heated at 100°C for 12h. After cooling to r.t., the mixture was diluted with H_2O, extracted with EtOAc. The EtOAc extract was washed with brine, dried(anhydrous $MgSO_4$) and concentrated *in vacuo*. Chromatography over silica gel and elution with hexanes:EtOAc(1:1) gave a solid residue. The residue was swished with EtOH to provide 1.6g(73%) of title compound.

^{1}H NMR (CD_3COCD_3) δ 1.82(6H, s), 3.18(3H, s), 7.50(1H, m), 8.00(4H, m), 8.50(1H, m), 8.60(1H, d).

Step 2: 3-(3-Amino-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

A mixture of 3-(4-methyl-4-nitro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one(1.5g, 3.7mmol), iron powder(1.5g, 27mmol) and NH4Cl(150mg) in 67% aqueous EtOH(45mL) was refluxed for 1h. The hot mixture was filtered through celite. Volatile solvent was evaporated *in vacuo*. The residue was suspended in water, filtered and dried under vacuum to give the title compound as a brown powder(1.4g, quantitative).

^{1}H NMR (CD_3COCD_3) δ1.76(6H, s), 3.18(3H, s),4.88(2H, brs), 6.86(1H, m), 7.10(1H, m), 7.35(1H, m), 7.98(4H, m).

Step 3: 3-(3-Chloro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

To a suspension of 3-(3-amino-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one(700mg, 1.7mmol) in 6M aqueous HCl(3mL) at 0°C was added dropwise a solution of 4M aqueous $NaNO_2$(500mL, 2.0mmol). After stirring for 30min, the diazotization mixture was added to a solution of CuCl(400mg, 4.0mmol) in concentrated HCl(2mL) at 0°C, then heated to 70-80°C for 10min, cooled to r.t., diluted with H_2O and extracted with EtOAc. Chromatography over silica gel and elution with hexanes:EtOAc(1:1) to give a solid residue(100mg). Recrystallization from EtOH provided the pure title compound(90mg, 13%).

^{1}H NMR (CD_3COCD_3) δ 1.80(6H, s), 3.16(3H, s), 7.20(1H, m), 7.94(2H, d), 7.98(1H, m), 8.05(2H, d), 8.10(1H, m).

EXAMPLE 124

3-(4-Fluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-propyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-1-pentanone and 4-fluorophenol.

^{1}H NMR(CD_3COCD_3) δ 0.94(3H, t), 1.38(2H, m), 1.78(3H, s), 2.05(2H, m) 3.14(3H, s), 7.08(4H, m), 7.92(2H, d), 8.02(2H, d).

EXAMPLE 125

3- (Diethyl amino)-5,5- dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

Step 1: 2-(diethyl amino) acetic acid 2-methyl-1-(4-(methylsulfonyl) phenyl) propan -1- one-2- yl ester

To a room temperature solution of 2-chloroacetic acid 2-methyl-1-(4-methylsulfonyl)phenyl)propan -1- one-2- yl ester (2.00 g, 6.27 mmol) in acetonitrile (10 mL) was added diethyl amine (1.62 mL, 15.7 mmol). The resulting solution was heated to 60°C for 16 hours. The reaction mixture was cooled to room temperature and partitioned between dichloromethane and water. The organic layer was separated, washed with brine, filtered through cotton and the solvent was evaporated under vacuum. Purification by silica gel chromatography (80% EtOAC/ Hex.) provided 1.70 g of the title compound.

^{1}H NMR (CD_3COCD_3) δ 0.85 (6H,t), 1.70 (6H, s), 2.37 (4H, q), 3.15 (3H,s) 3.27 (2H,s), 8.00 - 8.07 (2H,m), 8.15- 8.22 (2H,m).

Step 2: 3- (Diethyl amino)-5,5- dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

Sodium hydride, 60% dispersion (0.478 g, 11.96 mmol) was washed in hexane and suspended in DMF (5mL). This suspension was added to a 0°C solution of 2-(diethyl amino) acetic acid 2-methyl-1-(4-(methylsulfonyl) phenyl) propan -1- one-2- yl ester (1.70 g, 4.78 mmol) in DMF (20 mL). The resulting mixture was warmed to RT for 15 minutes. The mixture was diluted with ethyl acetate and quenched with water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to dryness. The residue was purified by swishing in ether/ hexanes to give 500 mg of crystalline solid on filtration.

^{1}H NMR (CD_3COCD_3) δ 0.95 (6H, t), 1.45 (6H,s), 3.07 (4H,q), 3.17 (3H,s), 7.65-7.70 (2H,m), 7.97- 8.05 (2H,m).

EXAMPLE 127

5,5-dimethyl-4-(4-methylsulfonyl-phenyl)-3-(3,5-dichloro-pyridin-2-yloxy)-5H-furan-2-one

To a R.T. solution of 2-chloroacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester (954 mg, 3 mmol, example 25) in acetonitrile (15 mL) was added 3,5-dichloro-2-pyridone (656 mg, 4.0 mmol) followed by DBU (2.28 g, 15 mmol) and the mixture was slowly warmed up to gentle reflux for 2 hours. The mixture was cooled to 25°C the volatiles were removed *in vacuo*. The residue was purified on silica gel chromatography (1/1, EtOAc/Hexanes then 100% EtOAc)) to provide the title compound.

Analysis calculated for $C_{18}H_{15}Cl_2NO_5S$: C, 50.48; H, 3.53; N, 3.27.
Found: C, 50.53; H, 3.49; N, 3.21.

EXAMPLE 128

(5R)-3-(4-Bromophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 117, the title compound was prepared from 4-bromophenoxyacetic acid and (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenylbutan-1-one.

^1H NMR(CD_3COCD_3) δ 0.93(3H, t), 1.78(3H, s), 2.12(2H, q), 3.15(3H, s), 7.05(2H, d), 7.50(2H, d), 7.94(2H, d), 8.05(2H, d).

EXAMPLE 129

(5R)-3-(4-Methoxyphenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)-phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from (2R)-2-chloroacetoxy-2-methyl-1-(4-

methylsulfonyl)phenylbutan-1-one (prepared similarly to the compound of Example 5 step 1) and 4-methoxyphenol.

^{1}H NMR(CD_3COCD_3) δ 0.92(3H, t), 1.75(3H, s), 2.08(2H, q), 3.14(3H, s), 3.74(3H, s), 6.83(2H, d), 6.97(2H, d), 7.89(2H, d), 7.99(2H, d).

EXAMPLE 130

(5R)-3-(5-Chloro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Step 1: 2-(S)-t-butyl-5-(R)-methyl-5-(2,2,2-trifluoroethyl)-1,3-dioxolan-4-one

To a solution of lithium diisopropylamide (prepared from 13 ml of diisopropylamine and 54 ml of 1.6 M n-BuLi in hexanes in 200 ml of anhydrous THF at 0°C) at -72°C was added slowly 2-(s)-t-butyl-5-(s)-methyl-1,3-dioxolan-4-one (12.95 g, 81.9 mmol, *Tetrahedron* , **1984**, *40*, 1313) at such a rate as to maintain the internal temperature below -60°C and the mixture was aged at -72°C for an hour. 1,1,1-Trifluoro-2-iodoethane (25 g, 119 mmol) was added quickly, the reaction temperature increased to -45°C and the mixture was aged at -72°C for 45 min. and then allowed to warm up to -20°C over 20 min. Saturated aq. NH_4Cl was then added and the product was extracted in i-PrOAc, dried over Na_2SO_4, concentrated and distilled under reduced pressure to afford 7.51 g of a brown oil BP 90°C / 20 mm Hg.
^{1}H NMR ($CDCl_3$, mixture of distereoisomers 3.2:1) d 0.97 (9H, 2s), 1.50 and 1.54 (3H, 2s), 2.59 (2H, m), 5.22 (1H, 2d).

Step 2: 2-(R)-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)-4,4,4-trifluoro-1-butanone

Using the procedures of Example 117 step 1, 2 and 3, the product of Step 1 was converted to the title compound.
^{1}H NMR ($CDCl_3$) δ 1.68 (3H, s), 2.72 (1H, m), 2.98 (1H, m), 3.08 (3H, s), 3.35 (1H, br s, OH), 8.03 (2H, d), 8.14 (1H, d).

Step 3: (2R)-2-Chloroacetoxy-2-methyl-1-(4-methylsulfonyl)-phenyl-4,4,4-trifluoro-butan-1-one

A mixture of (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluoro-1-butanone(5.2g, 16.8mmol), chloroacetic acid(2.0g, 21mmol), CMC(9.5g, 22mmol) and DMAP(100mg) in CH_2Cl_2(50mL) was stirred at r.t. for 2h. TLC showed the esterification completed. The mixture was washed with H_2O(2x), dried(anhydrous $MgSO_4$) and concentrated *in vacuo*. Chromatography over silica gel and elution with hexanes:EtOAc(1:1) gave 6.0g(92%) of the title compound as an oil.

^1H NMR(CD_3COCD_3) δ 1.98(3H, s), 3.18(3H, s), 3.28(2H, m), 4.35(2H, m), 8.08(2H, d), 8.28(2H, d).

Step 4: (5R)-3-(5-Chloro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluoro-butan-1-one and 5-chloro-2-pyridinol.

^1H NMR(CD_3COCD_3) δ 1.94(3H, s), 3.16(3H, s), 3.24(2H, q), 7.20(1H, d), 7.95(1H, m), 7.98(2H, d), 8.04(2H, d), 8.16(1H, m).

EXAMPLE 133

3-(5-Chloro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-propyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl-1-pentanone (prepared in a fashion similar to that of the compound in example 1 step 1,2 and 3) and 5-chloro-2-pyridinol.

^{1}H NMR(CD_3COCD_3) δ 0.93(3H, t), 1.42(2H, m), 1.76(3H, s), 2.05(2H, m) 3.15(3H, s), 7.16(1H, d), 7.90(3H, m), 8.02(2H, d), 8.16(1H, m).

EXAMPLE 134

3-(1-Cyclopropyl-ethoxy)-5,5-dimethyl-4-(4-methyl sulfonyl)phenyl)-5H-furan-2-one

Step 1: (1-cyclopropyl-ethoxy)acetic acid

To a suspension of NaH (80% in oil) (15.7 g, 523 mmol) in THF (180 mL) at 0°C were added bromoacetic acid (28.0 g, 203 mmol) and a-methylcyclopropane methanol (10.0 g, 116 mmol). The resulting mixture was then stirred at 70°C. After a period of 18 h, the reaction mixture was poured over cold H_2O and the H_2O phase was extracted once with Et_2O. The water phase was acidified with HCl and extracted twice with Et_2O. The ether was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude oil was then purified by flash chromotography (40% EtOAc in hexane to 40% EtOAc in Hexane + AcOH) to provide 5.0 g of the title compound.

Step 2: 2-(1-Cyclopropylethoxy)acetic acid 2-methyl-1-(4-methylsulfonyl)phenyl)propan-1-one-2-yl ester

A mixture of (1-cyclopropyl-ethoxy) acetic acid (1.0 g, 6.90 mmol; Example 134, Step 1) 2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl) propan-1-one (1.37 g, 5.76 mmol; Example 1, Step 3), CMC (8.90 g, 20.8 mmol) and DMAP (100 mg, 0.820 mmol) in CH_2Cl_2 (100 ml) was left at r.t. for a period of 18h. The resulting mixture was partitioned between NH_4OAc (20%) and CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting mixture was purified by flash chromatography (35% EtOAc in hexane) to provide 590 mg of the title compound.

Step 3: 3-(1-Cyclopropylethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one

To a solution of 2-(1-cyclopropyl-ethoxy)acetic acid 2-methyl-1-(4-(methyl sulfonyl)phenyl) propan-1-one-2-yl ester (590 mg, 1.60 mmol; Example 134, Step 2) CH_3CN (20 mL) were added isopropyl trifluoro acetate (294 mL, 2.07 mmol) and DBU (782 mg, 5.14 mmol). After a period of 18 h at 70°C. The reacting mixture was evaporated under reduced pressure and purified by flash chromatography (30% EtOAc in toluene) to provide 270 mg of the title compound. ^1H NMR (CD_3COCD_3) δ 0.20 to 0.50 (5H, m), 0.90 (1H, m), 1.35 (3H, d), 1.65 (6H, s), 3.20 (3H, s), 4.35 (1H, quintet), 8.10 (4H, m).

EXAMPLE 136

5-Methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-(propoxy)-5-(2, 2,2-trifluoroethyl)-5H-furan-2-one

Following the procedure described for Example 109, using 2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl)-4-trifluorobutan-1-one the title compound was obtained.

Step 2: 3-hydroxy-5-methyl-4-(4-(methylsulfonyl)phenyl-5-(2-trifluoroethyl)-5H-furan-2-one

^1H NMR (CD_3COCD_3) δ 1.30 (6H, 2d), 1.80 (3H, s), 3.15 (3H, s), 3.15 to 3.40 (2H, m), 5.30 (1H, quintet), 8.10 (4H, m).

EXAMPLE 140

5(R)-5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one

The title compound was prepared as described in Example 109, Step 2 using (5R)-5-ethyl-3-hydroxy-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one, which was prepared from the compound of Example 117, Step 3 following the procedure of Example 109, Step 1.

^{1}H NMR (CD_3COCD_3) δ 0.75-0.83 (3H,m), 1.24-1.30 (6H, m), 1.67 (3H, s), 2.01-2.08 (2H, m), 3.18 (3H, s), 5.17-5.27 (1H, m), 8.00-8.07 (4H, m).

EXAMPLE 141

5,5-Dimethyl-3-(2,2-dimethylpropyloxy)-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

To a mixture of 5,5-dimethyl-3-hydroxy-4-(4-(methylsulfonyl)phenyl-5H-furan-2-one (500 mg, 1.77 mmol, Example 109, Step 1) in DMF (6 mL) were added NaH (65 mg, 1.2 eq.), and neopentyl iodide (585 μL). After a period of 18 h at 70 °C, the reaction mixture was diluted with EtOAc. The mixture was washed with H_2O and the organic phase separated, dried over $MgSO_4$ and evaporated under reduced pressure. The resulting oil was purified by flash chromatography to provide the title compound (124 mg) as a white solid after precipitation with Et_2O.

^{1}H NMR (CD_3COCD_3) δ 0.95 (9H, s), 1.65 (6H, s), 3.15 (3H, s), 4.00 (2H, s), 8.00 (4H, m).

EXAMPLE 143

5(R) 3-(1-cyclopropyl-ethoxy)-5-ethyl-5-methyl-4-(4-(methyl sulfonyl)phenyl-5H-furan-2-one

Step 1: (1-cyclopropylethoxy)acetic acid 2(R)-methyl-1-(4-(methylsulfonyl)phenyl)butan-1-one-2yl ester

The title compound was prepared as described in Example 134 Step 2 using (1-cyclopropylethoxy)acetic acid and 2(R) 2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)butan-1-one from Example 117, Step 3.

Step 2: 5(R) 3-(1-cyclopropylethoxy)-5-ethyl-5-methyl-4(4-(methylsulfonyl)phenyl-5H-furan-2-one

The title compound was prepared as described in Example 134 Step 3.

^{1}H NMR (CD_3COCD_3) δ 0.1-0.4 (4H, m), 0.75 (2H, m), 1.00 (1H, m), 1.40 (3H, dd), 1.70 (3H, s), 2.05 (2H, m), 3.20 (3H, s), 4.50 (1H, m), 8.05 (m, 4H).

EXAMPLE 144

5(S) 5-Ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl-3-(2-propoxy)-5H-furan-2-one

Step 1: (±) 2-Methyl-1-(4-methylsulfonylphenyl)-prop-2-en-1-ol

To a solution of 4-bromothioanisole (51 g) in THF (600 mL) cooled to -72°C was added dropwise a solution of n-BuLi (120 mL, 2.4 M in hexane) over a period of 30 min. The mixture was stirred at -78°C for 2 h and then a solution of methacrolein (20.3 g) in THF (50 mL) was added over a period of 5 min. The reaction mixture was warmed to -20°C over a period of 20 min. and then quenched with saturated NH_4Cl (200 mL) and H_2O (200 mL). The product was extracted with 500 mL of 1:1 hexane/EtOAc, and dried over $MgSO_4$. The extract was filtered and concentrated to give the title compound as a yellow oil (55 g).

Step 2: (±) 2-Methyl-1-(4-methylsulfonylphenyl)-prop-2-en-1-ol

To a solution of the product from Step 1 (55 g., crude) in MeOH (1L) cooled to 0°C was added a solution of Oxone® (190 g in 700 mL H_2O) over a period of 2 h. The mixture was stirred at 5°C for an additional 3 h and then filtered. The filtrate was concentrated to remove MeOH and the remaining aqueous mixture was extracted with 1L of 2:1 EtOAc/hexane. The extract was dried over $MgSO_4$ filtered and concentrated. The residue was purified by silica gel chromatography

eluted with 3:2 hexane/EtOAc to give the title compound (22 g) as a colorless oil.

Step 3: (S)-2-Methyl-1-(4-methylsulfonylphenyl)-prop-2-en-1-ol

To a solution of dry 4A molecular sieves (20 g), and Ti $(O_2Pr)_4$ (24.8 mL) in CH_2Cl_2 (1L) cooled to -25°C was added dropwise (+)-diisopropyltartrate (22.4 mL). After stirring at -25°C for 30 min., a solution of (±)-2-methyl-1-(4-methylsulfonylphenyl)-prop-2-en-1-ol (21 g) in 500 mL of CH_2Cl_2 was added dropwise, followed by a solution of t-butyl hydroperoxide (20 mL, 5M in decane). The reaction mixture was stirred at -25°C for 5 h and then quenched with 500 mL of 10% aqueous solution of tartaric acid. After stirring for 1 h, the CH_2Cl_2 layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography eluted first with 3:1 hexane/EtOAc followed by 1:2 hexane/EtOAc to give the title compound as a white solid (9 g).

Step 4: (R)-(2-Methyloxiran-2-yl)-(4-methanesulfonylphenyl)-methanol

Following the same procedure described in Step 3 using 15 g of 4A molecular sieves, 500 mL of CH_2Cl_2, 12.4 mL of $Ti(OiPr)_4$, 11.2 mL of (-)-diisopropyl tartrate, 20 mL of 5M tBuOOH in decane and 9.8 g of the product from Step 3, the title compound (7.6 g, white solid) was obtained.

Step 5: (R)-[(1-Ethoxy-ethoxy)-(4-methanesulfonylphenyl)-methyl]-2-methyloxirane

To a solution of the product from Step 4 (7.2 g) and ethylvinyl ether (50 mL) in 200 mL of CH_2Cl_2 cooled to 0°C was added 50 mg of camphorsulfonic acid. The reaction mixture was stirred at r.t. for 20 min. and then treated with 1 mL of Et_3N, concentrated to give the crude title compound (9g).

Step 6: (R,S)-1-(1-Ethoxy-ethoxy)-2-methyl-1-(4-methylsulfonylphenyl) -butan-2-ol

To a suspension of CuI(20 g) in EtO (450 mL) cooled at -40°C was added dropwise a solution of MeLi (150 mL, 1.4 M in Et_2O). After stirring at -40°C for 20 min., a solution of the crude product from Step 7 (9 g) in 50 mL of Et_2O was added. The reaction mixture was stirred at -40°C for 30 min. and then quenched with 20 mL of MeOH and 300 mL of saturated NH_4Cl solution. Air was bubbled into the mixture with stirring at r.t. for 1 h. The resulting mixture was then extracted with 400 mL of Et_2O and the Et_2O extract was dried over $MgSO_4$ and concentrated to give the crude title compound (10 g) which was used for next step without further purification.

Step 7: (R.S)-2-Methyl-1-(4-methylsulfonylphenyl)-butane-1,2-diol

A solution of the crude product from Step 8 (10 g) in 200 mL of THF, 50 mL of AcOH and 50 mL of H_2O was heated at 50°C for 15 h. The mixture was then concentrated to give the crude title compound (7 g) which was used for next step with further purification.

Step 8: (S)-2-Hydroxy-2-methyl-1-(4-methylsulfonylphenyl)-butan-1-one

To a solution of the crude product from Step 7 (7 g) and $(Bu_3Sn)_2O$ (30 mL) in 150 mL of CH_2Cl_2 cooled at 10°C was added a solution of Br_2 (9.3 g in 30 mL of CH_2Cl_2). After stirring at r.t. for 30 min. the mixture was diluted with a solution of KF (500 mL, 3N) and 500 mL of Et_2O. The solid generated was removed by filtration and the filtrate was separated. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography eluted with 1:1 hexane/EtOAc to give 5 g of the title compound as a yellow oil.

^1H NMR (acetone-d_6) δ 8.31 (2H, d), 8.00 (2H, d), 4.67 (1H, s), 3.18 (3H, s), 2.00 (1H, m), 1.30 (1H, m), 1.50 (3H, s), 0.90 (3H, t).

Step 9: 5(S) 5-ethyl-S-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one

The title compound was prepared as described in Example 1 Step 4 using 2-propoxyacetic acid and 2(S) 2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl) butan-1-one.

^{1}H NMR (CD_3COCD_3) δ 0.75-0.83 (3H,m), 1.24-1.30 (6H, m), 1.67 (3H, s), 2.01-2.08 (2H, m), 3.18 (3H, s), 5.17-5.27 (1H, m), 8.00-8.07 (4H, m).

EXAMPLE 146 AND 147

3-(1-cyclopropylethoxy)-5,5-dimethyl-4-(4-(methyl sulfonyl)phenyl)-5H-furan-2-one (146) and 3-(1-cyclopropylethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one (147)

The racemate of Example 134 was separated on a HPLC CHIRALPAK AD (Daicel) column with 10% isopropanol in hexane.

EXAMPLE 148

3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl-5H-furan-2-one

Step 1: 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl-5H-furan-2-one

The title compound was prepared as described in Example 141 using 5,5-dimethyl-3-hydroxy-4-(4-(methylsulfonyl) phenyl-5H-furan-2-one and (bromomethyl)cyclopropane.

^{1}H NMR (CD_3COCD_3) δ 0.30 (2H, m), 0.55 (2H, m), 1.15 (1H, m), 1.60 (6H, s), 3.20 (3H, s), 4.20 (2H, d), 8.00 (4H, s).

EXAMPLE 149

5,5-dimethyl-3-(isobutoxy)-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

The title compound was prepared as described in Example 141 using 5,5-dimethyl-3-hydroxy-4-(4-(methylsulfonyl) phenyl-5H-furan-2-one and 1-bromo-2-methylpropane.

^{1}H NMR (CD_3COCD_3) δ 0.90 (6H, d), 1.65 (6H, d), 1.95 (1H, m), 3.20 (3H, s), 4.10 (2H, d), 8.00 (4H, m).

EXAMPLE 150

3-(4-Bromophenoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 1, the title compound was prepared from bromophenoxy acetic acid.

M.P.: 150-152°C ^{1}H NMR (CD_3COCD_3) δ 1.77 (6H, s), 3.15 (3H, s), 7.07 (2H, d), 7.46 (2H, d), 7.92 (2H, d), 8.02 (2H, d).

EXAMPLE 53

3-(6-Amino-2-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-6-aminopyridine.

M.P.: 165-166°C. ^{1}H NMR (CD_3COCD_3) δ 1.74 (6H, s), 3.14 (3H, s), 5.52 (2H, s, br), 6.17 (1H, d), 6.24 (1H, d), 7.41 (1H, t), 7.90 (2H, d), 8.02 (2H, d).

EXAMPLE 31

3-(2-Quinolinoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxyquinoline. M.P.:141-142°C.

^{1}H NMR (CD_3COCD_3) δ 1.83 (6H, s), 3.11 (3H, s), 7.26 (1H, m), 7.52 (1H, m), 7.70 (1H, m), 7.77 (1H, m), 7.93 - 8.02 (5H, m), 8.39 (1H, s).

EXAMPLE 50

3-(2-Chloro-5-pyridyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 2-chloro-5-hydroxypyridine.
M.P.: 196-197°C

^{1}H NMR (CD_3COCD_3) δ 1.78 (6H, s), 3.16 (3H, s), 7.33 (1H, m), 7.68 (1H, m), 7.94 (2H, d), 8.04 (2H, d), 8.14 (1H, m).

EXAMPLE 159

3-(6-benzothiazolyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 6-hydroxybenzothiazole M.P.: 212°C.

^{1}H NMR (CD_3COCD_3) δ 1.79 (6H, s), 3.10 (3H, s), 7.34 (1H, s), 7.86 (1H, d), 7.93 - 8.00 (5H, m), 9.15 (1H, s).

EXAMPLE 160

3-(6-Chloro-2-pyridiloxy)-5,5-dimethyl-4-(4-(methylsulfonyl) phenyl)-5H-furan-2-one

Following the procedure described fro Example 25, the title compound was prepared from 6-chloro-2-hydroxypyridine M.P.: 119-121°C.

^{1}H NMR (CD_3COCD_3) d 1.78 (6H, s), 3.15 (3H, s), 7.10 (1H, d), 7.25 (1H, d), 7.89 - 8.06 (5H, m).

EXAMPLE 161

3-(4-Quinazolyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 4-hydroxyquinazoline. M.P.: 174 - 177°C.

^{1}H NMR (CD_3COCD_3) δ 1.76 (6H, s), 3.12 (3H, s), 7.58 (1H, t), 7.67 (1H, d), 7.76 (2H, d), 7.85 (1H, t), 8.03 (2H, d), 8.16 (1H, d), 8.22 (1H, s).

EXAMPLE 162

(5R)-3-(5-Fluoro-2-pyridyloxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)-phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenylbutan-1-one (prepared similarly to the compound of Example 5, Step 1 but using the 2-(R) compound of Example 117, Step 3) and 5-fluoro-2-hydroxy-pyridine. M.S.: (CI, CH4) m/z 392 $(M+H)^+$

^{1}H NMR (CD_3COCD_3) δ 0.95 (3H, t), 1.76 (3H, s), 2.12 (2H, m), 3.15 (3H, s), 7.18 (1H, m), 7.73 (1H, m), 7.91 (2H, d), 8.02 - 8.07 (3H, m).

EXAMPLE 163

(5R)-3-(4-Fluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl) phenyl-5H-furan-2-one

Following the procedure described in Example 1, Step 4, the title compound was prepared using (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenylbutan-1-one (Example 117, Step 3) and 4-fluorophenoxy acetic acid. M.P.: 96.8 - 97.4 °C.

^{1}H NMR (CD_3COCD_3) δ 0.92 (3H, t), 1.77 (3H, s), 2.11 (2H, q), 3.14 (3H, s), 7.08 - 7.11 (4H, m), 7.9 (2H, d), 8.02 (2H, d).

EXAMPLE 164

(5R)-3-(5-Fluoro-2-pyridyloxy)-5-methyl-4-(4-methylsulfonyl) phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluorobutan-1-one (Example 130, Step 3) and 5-fluoro-2-hydroxypyridine.

^{1}H NMR (CD_3COCD_3) δ 1.94 (3H, s), 3.15 (3H, s), 3.24 (2H, q), 7.20 (1H, m), 7.75 (1H, m), 7.98 - 8.07 (5H, m).

EXAMPLE 165

3-(1-Isoquinolinyloxy)-5,5-dimethyl-4-(methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared using 1-hydroxyisoquinoline.
M.P.: 193.5 - 194.5

^{1}H NMR (CD_3COCD_3) δ 1.75 (6H, s), 3.12 (3H, s), 6.57 (1H, d), 7.27 (1H, d), 7.50 - 7.76 (5H, m), 8.02 (2H, d), 8.24 (1H, d).

EXAMPLE 166

(5R)-3-(4-fluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Following the procedure described in Example 1, Step 4, the title compound was prepared using 2-(R)-hydroxy-2-methyl-1-(4-

(methylsulfonyl)phenyl)-4,4,4-trifluoro-1-butanone (Example 130, Step 2) and 4-fluorophenoxyacetic acid. M.P.: 104.7 - 107.0°C

^{1}H NMR (CD_3COCD_3) δ 1.94 (3H, s), 3.15 (3H, s), 3.27 (2H, m), 7.07 - 7.13 (4H, m), 7.98 - 8.04 (4H, m), M.S.: (CI, CH_4) m/z 463 $(M+H)^+$

EXAMPLE 167

3-(3-Fluoro-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl) phenyl-5H-furan-2-one

Following the procedure described for Example 5, the title compound was prepared using 3-fluoro-2-hydroxypyridine M.P.: 156 - 157°C

^{1}H NMR (CD_3COCD_3) δ 1.78 (6H, s), 3.14 (3H, s), 7.23 (1H, m), 7.72 (1H, m), 7.91 (2H, d), 7.96 (1H, d), 8.03 (2H, d).

EXAMPLE 168

(5R)-3-(3,4-difluorophenoxy)-5-methyl-4-(4-methylsulfonyl) phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluorobutan-1-one (Example 130, Step 3) and 3,4-difluorophenol.

EXAMPLE 169

(5R)-3-(5-chloro-2-pyridyloxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl) phenyl-5H-furan-2-one

To a solution of 2-(R)-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)-1-butanone (800 mg, 30 mmol), Example 117, Step 3, in 24 mL of acetonitrile was added chloroacetic acid (383 mg), CMC (1.7 g) and DMAP (20 mg). The mixture was then stirred at r.t. for

4 hours. Then 5-chloro-2-hydroxypyridine (602 mg) and DBU (1.85 mL) were added and the mixture was stirred for 18 hours. Water was then added to the mixture which was extracted with CH_2Cl_2, then washed with 1N Hcl, brine, dried over MgSO4, filtered and the solvent evaporated under vacuum purification by flash chromatography on silica gel 40% EtOAc/Hexane afforded the title compound. M.P.: 191°C

^1H NMR (CD_3COCD_3) δ 0.95 (3H, t), 1.76 (3H, s), 2.11 (2H, m), 3.15 (3H, s), 7.18 (1H, d), 7.89 - 7.93 (3H, m), 8.03 (2H, d), 8.16 (1H, d).

EXAMPLE 170

3-(3,4-difluorophenoxy)-5-methyl-5-trifluoromethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 2-Trifluoromethyl-2-trimethylsilyloxypropionitrile

A mixture of 1,1,1-trifluoroacetone (8.9 mL, 0.1 mmol), trimethylsilylcyanide (13.3 mL, 0.1 mmol) and zinc iodide (5 mg) was stirred for 18 hours, to afford the title compound.

Step 2: 2-Hydroxy-1-(4-methylthio)phenyl-2-trifluromethyl propanone

To a solution of 4-bromothioanisole (19 g, 94 mmol) in THF (200 mL) at -78°C was added 1.33 M n-Butyl lithium (71 mL, 94 mmol). The mixture was stirred for 1 hr at -78°C then 10g (47 mmol) of the compound from Step 1 was added and the mixture was left to warm to r.t. The reaction mixture was quenched with 25% NH4OAc extracted with EtOAc, washed with brine, dried over MgSO4, filtered and the solvent evaporated to afford 9.7 g of the title compound.

Step 3: 2-Hydroxy-1-(4-methylsulfonyl)phenyl-2-trifluoromethyl propanone

Following the procedure described in Example 117, Step 3, and using the compound from the previous step, the title compound was obtained.

Step 4: 3-(3,4-difluorophenoxy)-5-methyl-5-trifluoromethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described in Example 1, Step 4, and using the compound obtained in the previous step, the title compound was obtained. M.P.: 154.1°C

^{1}H NMR (CD_3COCD_3) δ 2.06 (3H, s), 3.15 (3H, s), 6.98 (1H, s)7.7 (1H, m), 7.26 (1H, dd), 7.77 (2H, d), 8.02 (2H, d).

EXAMPLE 171

3-(3,4-Difluorophenoxy)-5-methyl-4-(4-(methylsulfonyl)phenyl)-5-propyl-5H-furan-2-one

Step 1: 2-Methyl-1-(4-methylthiophenyl)-pentan-1-one

Following the procedure described for Example 1, Step 1, the title compound was prepared from 2-methyvaleryl chloride and thioanisole.

Step 2: 2-Hydroxy-2-methyl-1-(4-methylthiophenyl)-pentan-1-one

Following the procedure described for Example 1, Step 2, the title compound was prepared from the product obtained in Step 1.

Step 3: (3,4-Difluorophenoxy)-acetic acid 1-methyl-1-(4-methythiobenzoylbutyl)ester

A solution of 3,4-difluorophenoxyacetic acid (0.38 g), the product from Step 2 (0.24 g), CMC (1.0 g), and DMAP (100 mg) in 5 mL of CH_2Cl_2 was stirred at r.t. for 15h. The reaction mixture was then treated with saturated solution of $NaHCO_3$ (20 mL) and extracted with 1:1 EtOAc/hexane (100 mL). The organic layer was dried over $MgSO_4$

filtered and concentrated to give the crude product which was used for next step without further purification.

Step 4: (3,4-Difluorophenoxy)-acetic acid 1-methyl-1-(4-methysulfonylbenzoylbutyl ester

A solution of the crude product from Step 3 in 50 mL of 10:1 CH_2Cl_2/MeOH (v/v) was treated with MMPP (1.0 g). The mixture was stirred at r.t. for 30 min. and then diluted with saturated $NaHCO_3$ solution (50 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was dried over $MgSO_4$, filtered and concentrated to give the title compound as a white solid.

Step 5: 3-(3,4-Difluorophenoxy)-5-methy-4-(4-(methylsulfonyl) phenyl)-5-propyl-5H-furan-2-one

A solution of the product from Step 4, CF_3CO_2iPr (0.5 mL) and DBU (0.2 mL) in CH_3CN (30 mL) was heated to reflux for 30 min. The mixture was then cooled to r.t. treated with ACOH (1 mL) and concentrated. The residue was dissolved in 2:1 EtOAc/hexane (20 mL) and filtered through a pad of silica gel. The filtrate was concentrated and the residue was stirred at 5°C 5:1 hexane/EtOAc (10 mL) for 15 h. The title compound was isolated by filtration as a white solid (380 mg).

^1H NMR (acetone-d_6) δ 8.04 (2H, d), 7.93 (2H, d), 7.28 (1H, m), 7.12 (1H, m), 6.92 (1H, m)(, 3.15 (3H, s), 2.06 (2H, m), 1.79 (3H, s), 1.80 - 1.96 (2H, m), 0.92 (3H, t).

EXAMPLE 174

3-Cyclobutyloxy-5,5-dimethyl-4-(4-methylsulfonylphenyl-5H-furan-2-one

Following the procedure described for Example 14, the title compound was obtained using cyclobutyloxyacetic acid. M.P. 111 - 112°C; Ms (Cl, CH_4) m/z 337 $(M+H)^+$; anal, calcd for $C_{17}H_{20}O_5S$: C, 60.70; H, 5.99; S, 9.53; found: C, 60.39; H, 6.05; S, 9.60.

EXAMPLE 175

3-(1-Indanyloxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 14, the title compound was obtained using 1-indanyloxyacetic acid. M.p. 128 - 129°C; MS (Cl, CH_4) m/z 398 $(M+H)^+$; and anal. calcd. for $C_{22}H_{22}O_5S$: C, 66.31; H, 5.56; S, 8.05; found: C, 66.27; H, 5.47; 5, 8.34.

EXAMPLE 176

3-(2-Indanyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one

Following the procedure described for Example 14, the title compound was obtained using 2-indanyloxyacetic acid. M.p. 142-143°C; Ms (Cl, CH_4) m/z 3.99 $(M+H)^+$; anal. calcd. for $C_{22}H_{22}O_5S$: C, 66.31; H, 5.56; found: C, 66.50; H, 5.64.

EXAMPLE 177

3-Cyclopentyloxy-5,5-dimethyl-4-(4-methylsulfonylphenyl)5H-furan-2-one

Following the procedure described for Example 109 the title compound was prepared from cyclopentyl bromide. M.P.: 121 - 122°C.

^1H NMR (CD_3COCD_3) δ 1.55 - 1.85 (8H, m), 1.65 (6H, s), 3.15 (3H, s), 5.43 (1H, m), 7.98 - 8.07 (4H, m).

EXAMPLE 178

3-(3,3-Dimethylcyclopentyloxy)-5,5-dimethyl-4-(4-methylsulfonyl-phenyl)-5H-furan-2-one

Step 1: 3,3-Dimethylcyclopentanol

To a solution of 4,4-Dimethyl-2-cyclopenten-1-one (1.65 g, 15 mmol) in EtOAc (50 mL) was added palladium on activated carbon (270 mg). The resulting suspension was vigorously stirred under an hydrogen atmosphere for 22 hours. The reaction was diluted with CH_2Cl_2 (150 mL) and filtered on a pad of silica gel washed with EtOAc. The solvents were removed by distillation under atmospheric pressure using a 15 cm Vigreux column. The distillation residue was dissolved in MeOH (50 mL) cooled to 0°C and sodium borohydride (304 mg, 8 mmol) was added and te reaction mixture was stirred at r.t. for 24 h. The reaction was diluted with NH4OAc eq. 25% w/r and extract with EtOAc. The organic layer was separated, dried over $MgSO_4$ and concentrated. Purification by silica gel chromatography (50% Et2O/pentane) provided 1.14 g of the title compound as a colorless liquid.

^1H NMR (CD_3COCD_3) δ 0.94 (3H, s)1.07 (3H, s). 1.25 - 1.4 (2H, m), 1.55 - 1.63 (2H, m), 1.67 (1H, dd), 1.85 - 1.95 (1H, m), 3.42 (1H, d), 4.27 (1H, m).

Step 2: 3-Iodo-1,1-dimethylcyclopentane

To a 0°C solution of 3,3-Dimethylcyclopentanol (Step 1) (1.14 g, 10 mmol) and triethylamine (2.0 mL, 14.3 mmol) in dichloromethane was added dropwise methanesulfonyl chloride (1.0 mL, 12.9 mmol). The reaction was allowed to proceed for 30 min. at 0°C, then it was diluted with water and extracted twice with CH_2Cl_2. The combined organic layers were dried over MgSO4 and concentrated in vacuo. The resulting residue was dissolved in acetone (50 mL), cooled to 0°C and lithium iodide (6.68, 50 mmol) was added). The resulting suspension was stirred at r.t. for 20 hours. Most of the solvent was removed in vacuo, the residue was taken in EtOAc and washed twice with water. The organic layer was dried over $MgSO_4$ and concentrated. This crude product was purified by flash chromatography eluted with 40 Et2O/pentane to give the title compound as a colorless oil.

^{1}H NMR (CD_3COCD_3) δ 0.98 (3H, s), 1.14 (3H, s), 1.38 - 1.46 (1H, m), 1.57 - 1.64 (1H, m), 1.93 (1H, dd), 2.06 - 2.16 (2H, m), 2.29 (1H, m), 4.38 (1H, quintet)

Step 3:

Following the procedure described for Example 109, the title compound was prepared from 3-iodo-1,1-dimethylcyclopentanol (Step 2). M.P.: 99 - 100°C.

^{1}H NMR (CD_3COCD_3) δ 0.93 (3H, s), 0.99 (3H, s), 1.32 - 1.40 (1H, m), 1.48 - 1.62 (2H, m), 1.65 (6H, s), 1.74 (1H, dd), 1.78 - 1.88 (1H, m), 1.93 - 2.02 (1H, m), 3.17 (3H, s), 5.90 (1H, m), 8.02 (4H, dm).

EXAMPLE 179

3-Isopropoxy-5-methyl-4-(4-methylsulfonylphenyl)-5-propyl-5H-furan-2-one

Following the procedure described for Example 171, the title compound was prepared from isopropoxyphenyl acetic acid. M.P.: 95 - 96°C.

^{1}H NMR (CD_3COCD_3) δ 0.88 (3H, t), 1.12 - 1.32 (2H, m), 1.28 (6H, 2d), 1.67 (3H, s), 2.00 (2H, m), 3.17 (3H, s), 5.22 (1H, heptet), 8.04 (4H, s).

EXAMPLE 180

3-(2-Methoxy-5-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 5-Hydroxy-2-methoxypyridine

To 6M aqueous HCl(20mL) at 00C was added 5-amino-2-methoxypyridine(3.1g, 25mmol), stirred for 10min and a solution of 4M

aqueous NaNO2(7mL, 28mmol) was added dropwise over a period of 10min. After further stirring for 30min, 60%HPF6(2mL) was added and precipitate formed immediately. The mixture was stirred for 15min, H2O(50mL) was added. The precipitate was collected, washed with H2O(3x) and dried under vacuum to give the corresponding diazonium salt as brown powders(6.5g, 92%).

The above diazonium salt in acetic anhydride(25mL) was heated at 100-1100C for 1h. Solvent was evaporated in vacuo. The residue was diluted with H2O and extracted with Et2O. Solid residue was filtered and the ethereal layer was separated, washed with saturated aq. NaHCO3 brine, dried(anhydrous MgSO4) and concentrated to provide the 5-acetoxy-2-methoxypyridine as a brown oil(600mg).

^{1}H NMR(CD3COCD3) δ 2.26(3H, s), 3.85(3H, s), 6.78(1H, d), 7.48(1H, dd), 7.92(1H, d).

To a solution of the 5-acetoxy-2-methoxypyridine(600mg, 3.59mmol) in MeOH(10mL) was added 1M aq. NaOH(10mL, 10mmol). After stirring at r.t. for 30min, volatile solvent was removed in vacuo, acidified with HOAc and extracted with CHCl3(3x). The combined CHCl3 extracts were washed with H2O, dried(anhydrous MgSO4) and evaporated to give the title compoud as a brown oil(240mg, solidified on standing).

^{1}H NMR(CD3COCD3) δ 3.78(3H, s), 6.60(1H, d), 7.20(1H, dd), 7.70(1H, d), 8.20(1H, br s).

Step 2: 3-(2-Methoxy-5-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 5-hydroxy-2-methoxypyridine.

^{1}H NMR(CD$_3$COCD$_3$) δ 1.75(6H, s), 3.16(3H, s), 3.85(3H, s), 6.66(1H, d), 7.47(1H, dd), 7.90(2H, d), 7.95(1H, d), 8.04(2H, d).

EXAMPLE 181

3-(5-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 2-Hydroxy-5-methylpyridine

Following the procedure described for Example 48, step 1, the title compound was prepared from 2-amino-5-picoline.

^{1}H NMR(CD_3COCD_3) δ 2.05(3H, s), 6.36(1H, d), 7.24(1H, d), 7.35(1H, dd).

Step 2: 3-(5-Methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 2-hydroxy-5-methylpyridine.

^{1}H NMR(CD_3COCD_3) δ 1.75(6H, s), 2.28, 3.16(3H, s), 6.98(1H, d), 7.68(1H, dd), 7.90(2H, d), 7.96(1H, d), 8.04(2H, d).

EXAMPLE 184

(5RS)-3-(3,4-Difluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Step 1: 2(RS)-2-Methyl-1-(4-(methylthio)phenyl)-4,4,4-trifluoro-1-butanone

Following the procedure described for example 1, step 1, the title compound was prepared from 2(RS)-2-methyl-4,4,4-trifluoro-butryl chloride(GB 2238790-A) and thioanisole.

^{1}H NMR(CD3COCD3) δ 1.22(3H, d), 2.30(1H, m), 2.52(3H, s), 2.82(1H, m), 3.88(1H, m), 7.35(2H, d), 7.92(2H, d).

Step 2: 2-(RS)-2-Hydroxy-2-methyl-1-(4-(methylthio)phenyl)-4,4,4-trifluoro-1-butanone

To 2-(RS)-2-hydroxy-2-methyl-1-(4-(methylthio)phenyl)-4,4,4-trifluoro-1-butanone(12g, 45.8mmol) and triethyl phosphite(16mL) in DMF(250mL) at -10°C was added 1M t-BuOK(46mL, 46mmol) in t-BuOH and air was bubbled through the mixture for 3h. After quenching with 2.5M aq. HOAc(20mL), the mixture was diluted with H_2O, extracted with Et_2O. The etheral extract was washed with H_2O(2x), 0.5M aq. NaOH, dried(anhydrous $MgSO_4$) and concentrated. Chromatography over silica gel and elution with hexanes:EtOAc(4:1) gave the title compound as a yellow oil(6.0g, ~90% pure).

^1H NMR(CD_3COCD_3) δ 1.62(3H, s), 2.54(3H, s), 2.70-3.20(2H, m), 7.32(2H, d), 8.15(2H, d).

Step 3: 2-(RS)-2-Hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)-4,4,4-trifluoro-1-butanone

To a solution of 2-(RS)-2-hydroxy-2-methyl-1-(4-(methylthio)phenyl)-4,4,4-trifluoro-1-butanone(6.0g, 21.6mmol) in CH_3Cl(200mL) was added mCPBA(12g, Aldrich 27,303-1, 57-86%) at 0°C. The mixture was slowly warmed to r.t. over a period of 1h, washed with 1M aq. NaOH(2x), brine, dried(anhydrous $MgSO^4$) and concentrated. Chromatography over silica gel and elution with hexanes:EtOAc(2:1) provided the title compound(4.0g, 60%).

^1H NMR(CD^3COCD^3) δ 1.66(3H, s), 2.70-3.20(2H, m), 3.18(3H, s),5.35(1H, s), 8.04(2H, d), 8.30(2H, d).

Step 4: (5RS)-3-(3,4-Difluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Following the procedure described for example 1, step 4, the title compound was prepared from 3,4-difluorophenoxyacetic acid and 2-

(RS)-2-hydroxy-2-methyl-1-(4-(methylsulfonyl)phenyl)-4,4,4-trifluoro-1-butanone. NMR of the title compound is the same as Example 168.

EXAMPLE 185

3-(3-Chloro-4-methoxyphenoxy)-5,5-dimethyl-4-(4-methylsulfonyl)-phenyl-5H-furan-2-one

Step 1: 3-Chloro-4-methoxyphenoxyacetic acid

To a mixture of hydroquinone(24g, 0.22mol) and ethyl bromoacetate(24mL, 0.22mol) in DMF(300mL) was added 10M aq. NaOH(22mL, 0.22mol). The mixture was stirred at 0°C for 1h, diluted with H2O, acidified with 6M aq. HCl and extracted with EtOAc. The EtOAc extract was dried(anhydrous $MgSO_4$) and concentrated in vacuo. The residue was swished with Et2O to give ethyl 4-hydroxyphenoxy-acetate(5.8g) as a white powder.

Ethyl 4-hydroxyphenoxyacetate(1.5g, 7.6mmol) was reacted with SO_2Cl_2(1.5mL) to give ethyl 3-chloro-4-hydroxyphenoxyacetate (700mg, ~80% pure) as a white powder. To a solution of ethyl 3-chloro-4-hydroxyphenoxyacetate(700mg, 3.0mmol) and MeI(0.280mL, 4.5mmol) in DMF(5mL) at 0°C was added 10M aq.NaOH(0.320mL, 3.2mmol). The mixture was stirred at r.t. for 12h, then diluted with H_2O and extracted with EtOAc to give ethyl 3-chloro-4-methoxyphenoxy-acetate (700mg).

The above ethyl 3-chloro-4-methoxyphenoxyacetate (700mg) was hydrolysed with 1M aq. NaOH in THF-MeOH (30 mL, 2:1) to provide the title compound as a white powder.

^1H NMR(CD3COCD3) δ 3.84(3H, s), 4.70(2H, s), 6.85-7.10(3H, m).

Step 2: 3-(3-Chloro-4-methoxyphenoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for example 1, step 4, the title compound was prepared from 3-chloro-4-methoxyphenoxyacetic

acid and 2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl)propan-1-one(example 1, step 3).

^{1}H NMR(CD3COCD3) δ 1.75(6H, s), 3.14(3H, s), 3.84(3H, s), 6.95-7.20(3H, m), 7.86(2H, d), 8.00(2H, d).

EXAMPLE 186

(5R)-3-(3-Chloro-4-methoxyphenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 1, step 4, the title compound was prepared from 3-chloro-4-methoxyphenoxyacetic acid and (2R)-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-butan-1-one (Example 117, Step 3).

^{1}H NMR(CD3COCD3) δ 0.94(3H, t), 1.76(3H, s), 2.10(2H, q), 3.15(3H, s), 3.85(3H, s), 6.95-7.20(3H, m), 7.90(2H, d), 8.00(2H, d).

EXAMPLE 188

(5R)-3-(4-Chlorophenoxy)-5-(2, 2, 2-trifluoroethyl)-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 1, Step 4, the title compound was prepared from 4-chlorophenoxyacetic acid and (2R)-2-hydroxy -2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluoro-butan-1-one (Example 130, Step 2).

^{1}H NMR(CD_3COCD_3) δ 1.95 (3H, s), 3.15 (3H, s), 3.25 (2H, m), 7.12 (2H, d), 7.36 (2H, d), 8.02 (4H, m).

Analysis calculated for $C_{20}H_{16}ClF_3O_5S$: C, 52.13; H, 3.50.

Found: C, 52.27; H, 3.63.

EXAMPLE 189

(5R)-3-(4-Bromophenoxy)-5-(2, 2, 2-trifluoroethyl)-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 1, Step 4, the title compound was prepared from 4-bromophenoxyacetic acid and (2R)-2-hydroxy -2-methyl-1-(4-methylsulfonyl)phenyl-4,4,4-trifluoro-butan-1-one (Example 130, Step 2).

^{1}H NMR(CD_3COCD_3) δ 1.94 (3H, s), 3.15 (3H, s), 3.25 (2H, m), 7.07 (2H, d), 7.50 (2H, d), 8.02 (4H, m).

EXAMPLE 195

5-Cyclopropylmethyl-3-(3,4-difluorophenoxy)-5-methyl--(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 2-Cyclopropylmethyl-2-methyl-1-(4-thiomethyl)phenyl-propan-1-one

To a cold (-78 °C) solution of 1-(4-thiomethyl)phenyl-propan-1-one (900 mg, 5 mmol) in dry THF (15 mL) was added a solution of KHMDS (5.5 mmol, 11 mL). The mixture was warmed to r.t. for 5 min and then cooled to 0 °C. Bromomethylcyclopropane (810 mg, 6 mmol) was added. The mixture was warmed to r.t. and stirred for 20 h. Aqueous NH_4Cl solution was added. The mixture was extracted with EtOAc and the concentrated crude extract was purified by chromatography on silica gel (eluted with 20% EtOAc/hexane) to give 435 mg (37%) of the title compound.

Step 2: 2-Cyclopropylmethyl-2-methyl-1-(4-methylsulfonyl)phenyl-propan-1-one

To a solution of the product of step 1 (435 mg, 1.87 mmol) in a mixture of CH_2ClCH_2Cl (10 mL) and methanol (10 mL) was added MMPP (2.3 g 3.7 mmol) in 2 portions . The mixture was stirred at r.t. for

6 h. H_2O was added and the product was extracted with EtOAc. The extracts were washed with H_2O and brine, dried and concentrated to an oil. The crude oil was purified by chromatography on silica gel (eluted with 30% EtOAc/hexane) to give 363 mg (83%) of the title compound.

Step 3: -Cyclopropylmethyl-2-hydroxy-2-methyl-1-(4-methylsulfonyl)phenyl-propan-1-one

To a mixture of the product of step 2 (310 mg, 1.16 mmol), CCl_4 (268 mg, 1.74 mmol), Aliquat 336® (75 mg, 0.185 mmol) and toluene (293 mg, 3.19 mmol) was added powered NaOH (102 mg, 2055 mmol) in portions. Aqueous NH_4Cl solution was added. The mixture was neutralized with 1N HCl and extracted with EtOAc and the concentrated crude extract was purified by chromatography on silica gel (eluted with 30% EtOAc/hexane) to give 124 mg (38%) of the title compound.

Step 4: 5-Cyclopropylmethyl-3-(3,4-difluorophenoxy)-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 117, the title compound was prepared from the product of step 3 and 3,4-difluorophenoxyacetic acid.

^1H NMR(CD_3COCD_3) δ-.01 (1H, m), 0.19 (1H, m), 0.42 (1H, m), 0.51 (1H, m), 0.71 (1H, m), 1.82 (3H, s), 1.87 (1H, dd), 2.26 (1H, dd), 3.15 (3H, s), 6.95 (1H, m), 7.14 (1H, m), 7.29 (1H, q), 8.05 (4H, q).

EXAMPLE 196

(5R)-3-(3-Fluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 3-fluorophenol and (2R)-2-chloroacetoxy-2-methyl-1-(4-methylsulfonyl)phenyl -butan-1-one, prepared as in Example 162.

^{1}H NMR(CD_3COCD_3) δ 0.93 (3H, t), 1.79 (3H, s), 2.13 (2H, q), 3.15 (3H, s), 6.89 (3H, m), 7.46 (1H, q), 7.93 (2H, d), 8.05 (2H, d).

EXAMPLE 197

(5R)-3-(4-Chloro-3-fluorophenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 4-chloro-3-fluorophenoxyacetic acid and (2R)-2-chloroacetoxy -2-methyl-1-(4-methylsulfonyl)phenyl -butan-1-one.

^{1}H NMR(CD_3COCD_3) δ 0.94 (3H, t), 1.80 (3H, s), 2.13 (2H, q), 3.15 (3H, s), 6.95 (1H, m), 7.10 (1H, m), 7.48 (1H, t), 7.94 (2H, d), 8.04 (2H, d).

EXAMPLE 198

(5R)-3-(3-Phenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from phenol and (2R)-2-chloroacetoxy -2-methyl-1-(4-methylsulfonyl)phenylbutan-1-one, prepared as in Example 162.

^{1}H NMR(CD_3COCD_3) δ 0.94 (3H, t), 1.78 (3H, s), 2.15 (2H, q), 3.14 (3H, s), 7.09 (3H, m), 7.33 (2H, m), 7.93 (2H, d), 8.01 (2H, d).

Analysis calculated for $C_{20}H_{20}O_5S$: C, 64.50; H, 5.41.
Found: C, 63.94; H, 5.48.

EXAMPLE 199

(5R)-3-(4-Chloro-3-methylphenoxy)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 25, the title compound was prepared from 4-chloro-3-methylphenol and (2R)-2-chloroacetoxy -2-methyl-1-(4-methylsulfonyl)phenyl -butan-1-one, prepared as in Example 162.

^{1}H NMR(CD_3COCD_3) δ 0.93 (3H, t), 1.78 (3H, s), 2.12 (2H, q), 2.30 (3H, s), 3.15 (3H, s), 6.91 (1H, dd), 7.04 (1H, d), 7.30 (1H, d), 7.92 (2H, d), 8.02 (2H, d).

Analysis calculated for $C_{21}H_{21}ClO_5S$: C, 59.93; H, 5.03.
Found: C, 59.59; H, 5.02.

EXAMPLE 200

3-(4-Chloro-3-methylphenoxy)-5-5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Following the procedure described for Example 108, the title compound was prepared from 4-chloro-3-methylphenoxyacetic acid and 2-chloroacetoxy-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one.

^{1}H NMR(CD_3COCD_3) δ 1.76 (6H, s), 2.79 (3H, s), 3.15 (3H, s), 6.92 (1H, dd), 7.06 (1H, d), 7.28 (1H, d), 7.92 (2H, d), 8.02 (2H, d).

Analysis calculated for $C_{21}H_{19}ClO_5S$: C, 59.04; H, 4.71.
Found: C, 59.18; H, 4.78.

EXAMPLE 201

(5R)-3-(5-bromo-2-pyridyloxy)-4-(4-methylsulfonylphenyl)-5-methyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

Step 1: (5R)-4-methyl-4-(2,2,2-trifluoroethyl)-5-(4-methylsulfonyl-phenyl)-3,6-dioxabicyclo[3.1.0]hexan-2-one

To a 0 °C solution of the chloroacetate(1.16 g, 3 mmol) from step 3, Example 130, in acetonitrile(15 mL) was added DBU(0.491 mL, 3.3 mmol) and the mixture was warmed up to 25 °C. After 2 hours, the mixture was poured on icy 1N HCl and ethyl acetate; the organic layer was separated and the aquous further extracted once with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$ and the solvents were removed in vacuo to yield the essentially pure title compound(0.930 g).

^1H NMR (CD_3COCD_3) δ 1.60-1.70(3H, 2s), 2.50-3.05(2H, m), 3.13(3H, s), 4.40-4.30(1H, 2s), 7.95-8.05(4H, 2d).

Step 2: (5R)-3-(5-bromo-2-pyridyloxy)-4-(4-methylsulfonylphenyl)-5-methyl-5-(2,2,2-trifluoroethyl)-5H-furan-2-one

To a 0 °C mixture of the epoxide(0.930 g) from step 1 in dimethylformamide(3 mL) and isopropanol(12 mL) was added the potassium salt of 5-bromo-2-hydroxypyridine, prepared from 5-bromo-2-hydroxypyridine and one equivalent of 8N KOH followed by evaporation to dryness with toluene and high vacuum drying, (0.742 g, 3.5 mmol) and the mixture was warmed up slowly to reflux for 16 hrs. It was then cooled to room temperature and poured on icy dilute ammonium chloride and ethyl acetate; the organic layer was separated and the aquous further extracted ounce with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$ and the solvents were removed in vacuo to yield after purification on silica gel(10% acetone/toluene) the title compound (0.380 g).

^1H NMR (CD_3COCD_3) δ 1.90(3H,s), 3.15(3H,s), 3.15-3.30(2H,AB), 7.15(1H,d), 7.95-8.10(5H,m), 8.25(1H,d).

EXAMPLE 202

(5R)-3-(5-bromo-2-pyridyloxy)-4-(4-methylsulfonylphenyl)-5-ethyl-5-methyl-5H-furan-2-one

Step 1:

To a 25°C mixture of (2R)-chloroacetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)butan-1-one ester(0.896 g, 2.7 mmol prepared as in Example 162) and 5-bromo-2-hydroxypyridine(0.560 g, 3.2 mmol) in acetonitrile(20 mL) was added DBU(1.5 mL) and the mixture was warmed up to 70-80°C for 2 hrs. The volatils were then removed in vacuo and the mixture purified on silica gel(10% acetone/toluene) to yield the title compound(0.587 g)

^{1}H NMR (CD_3COCD_3) δ 0.90-1.0(3H,t), 1.75(3H,s), 2.00-2.15(2H,m), 3.15(3H,s) 7.10-7.15(1H,d), 7.85-8.05(4H,2d), 8.20-8.30(1H,d).

EXAMPLE 203

3-(5-Chloro-6-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Step 1: 3-(5-Nitro-6-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

A suspension made of the alcohol(2.82 g, 10 mmol) from step 1 Example 109, 3-nitro-6-chloro-2-picoline[C.A.**70**:114970s](2.06 g, 12 mmol) and 10N NaOH(1.1mL) in DMF(35 mL) was warmed up to to 105°C for 8 hrs. It was then cooled to room temperature and poured on icy H_2O and ethyl acetate. The pH was adjusted to c.a. 8 then the organic layer was separated and the aqueous further extracted ounce with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$ and the solvents were removed in vacuo to yield after purification on silica gel(10% acetone/toluene) the title compound (4.180 g).

^{1}H NMR (CD_3COCD_3) δ 1.75(6H,s), 2.70(3H,s), 3.15(3H,s), 7.15-7.20(1H,d), 7.85-8.05(4H,2d), 8.45-8.55(1H,d).

Step 2: 3-(5-Amino-6-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

A mixture of the compound from the previous step(3.19g, 7.6 mmol), ammonium chloride(0.250 g) and iron powder(3 g) in ethanol(50 mL) and H_2O(20 mL) was warmed up to reflux for 1.5 hrs after what it was filtered quickly, while hot, over celite. To the filtrate was added water(250 mL) and ethyl acetate. The organic layer was separated and the aquous further extracted ounce with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$ and the solvents were removed in vacuo to yield after purification by swish in diethyl ether the title compound (3.0 g).

^{1}H NMR (CD_3SOCD_3) δ 1.75(6H,s), 2.10(3H,s), 3.25(3H,s), 4.75-4.85 (2H,bs), 6.65-6.70(1H,d), 7.00-7.05(1H,d), 7.80-8.00(4H,2d).

Step 3: 3-(5-chloro-6-methyl-2-pyridyloxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl-5H-furan-2-one

Sodium nitrite(0.152 g, 2.2 mmol) in H_2O(1 mL) was added dropwise to a 0°C suspension of the compound(0.776 g) from the previous step in 6N HCl(4 mL) and the mixture was stirred at 0°C for 0.5 hr. It was then transfered dropwise into a CuCl(0.396 g, 4 mmol) solution in 12N HCl(3 mL). The reaction mixture was warmed up to 80°C for c.a. 10 min. then cooled to 25°C. The mixture was poured on icy H_2O and the pH adjusted to c.a. 4-5 then ethyl acetate was added. The organic layer was separated and the aquous further extracted ounce with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$ and the solvents were removed in vacuo to yield after purification by swish in diethyl ether the title compound (0.310 g).

^{1}H NMR (CD_3COCD_3) δ 1.75(6H,s), 2.40(3H,s), 3.15(3H,s),6.90-7.00(1H,d), 7.75-7.85(1H,d), 7.85-8.05(4H,2d).

EXAMPLE 207

3-(1-Cyclopropylethoxy)-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 3-Diazo-2,4-(3H, 5H)-furandione

To tetronic acid (5.00 g, 49.9 mmol) in CH2Cl2 (250 mL) at 0°C were added Et3N (8.3 mL, 59.6 mmol) and tosyl azide (7.37 g, 37.4 mmol). After a period of 2 h at r.t., the reaction mixture was partitioned between NH4OAc (25%) and CH2Cl2. The organic phase was dried over Na2SO4, filtered and evaporated under reduced pressure. The resulting mixture was purified by flash chromatography (20% to 35% EtOAc in Hexane) to provide 1.4 g of the title compound as a white solid.

Step 2: 3-(1-cyclopropylethoxy)-4-hydroxy-2(5H)-furanone

To the mixture of 3-diazo-2,4-(3H, 5H)-furandione (300 mg, 2.38 mmol; Example 207, Step 1) and α-methylcyclopropanemethanol (2.0 mL) was added rhodium acetate (30 mg). The mixture was heated at 130°C for a period of 18 h. The excess of alcohol was evaporated under reduced pressure and the resulting crude mixture was purified by flash chromatography (10% to 20% MeOH in CH2Cl2) to provide 50 mg of the title compound.

Step 3: 3-(1-cyclopropylethoxy)-4-(4-methylthio)phenyl)-5H-furan-2-one

To a mixture of 3-(1-cyclopropylethoxy)-4-hydroxy-2-(5H)furanone (50 mg, 0.27 mmol; Example 207, Step 2) and diisopropylethylamine (0.066 mL, 0.38 mmol) in CH2Cl2 (2.0 mL) at -20°C was added trifluoromethanesulfonic anhydride (0.060 mL, 0.36 mmol). After a period of 5 min. at -20°C, the reaction mixture was brought to 0°C then to r.t. The reaction mixture was partitioned between NH4OAc (25%) and CH2Cl2. The organic phase was dried over Na2SO4, filtered and evaporated under reduced pressure. The title compound was purified by flash chromatography to provide 30 mg of material.

Step 4: 3-(1-cyclopropylethoxy)-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one

To a mixture of 3-(1-cyclopropylethoxy)-4-(4-methylthio)phenyl)-5H-furan-2-one (30 mg, 0.10 mmol; Example 207, Step 3) in CH2Cl2 ((1.0 mL) MeOH (3.0 mL) were added an excess of OXONE® (150 mg). After the TLC showed completion, the reaction mixture was extracted with EtOAc. The organic phase was dried over Na2SO4 filtered and evaporated under reduced pressure. The title compound was purified by flash chromatography to provide 6 mg of material.

^{1}H NMR (CD3COCD3) δ 0.20 - 0.60 (4H,m), 1.10 (1H,m), 1.45 (3H,d), 3.20 (3H,s), 4.50 (1H,m), 5.30 (2H, s), 8.10 (4H, m).

EXAMPLE 208

3-(1-Cyclopropylmethoxy)-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one

The title compound was prepared as described in Example 207.

^{1}H NMR (CD3COCD3) δ 0.40 - 0.65 (4H,m), 1.30 (1H,m), 3.20 (3H,s), 4.30 (2H, d), 5.30 (2H, s), 8.05 (4H, m).

EXAMPLE 209

(RS) 5-Ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one

Step 1: (RS) -1-(4-Methylthiophenyl)-2-methyl-1-butanone

To a suspension of $AlCl_3$ (35.4 g) in $CHCl_3$ (500 mL) at -10°C was added dropwise 2-methylbutyryl chloride (31.3 g) followed by thioanisole (31.2 mL). The mixture was then stirred at r.t. for 20 min. and was then cooled back to 0°C. Water (200 mL) was then added over 30 min. The $CHCl_3$ layer was separated and dried over $MgSO_4$. After

filtration and removal of the solvent, the residue was dried under vacuum at 80°C for 2 h to give 35 g of the title compound.
^{1}H NMR (300 MHz, acetone d_6) δ 0.88 (3H, t), 1.12 (3H, d), 1.38 - 1.50 (1H, m), 1.70 - 1.85 (1H, m), 3.47 (1H, m), 7.32 - 7.40 (2H, m), 7.90 - 8.00 (2H, m).

Step 2: (RS)-2-Hydroxy-1-(4-methylthiophenyl)-2-methyl-1-butanone

To a mixture of the ketone from Step 1 (10 g, 48 mmol) and Aliquat® 336 (20 mL) in CCl_4 (40 mL) and toluene (80 mL) at r.t. was added NaOH pellets (3.8 g, 96 mmol). While stirring vigourously, the mixture was heated briefly to reflux and was then stirred overnight at r.t. After partitioning between CH_2Cl_2 and H_2O, the whole was filtered through celite. The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash chromatography (1:10 EtOAc:hexane) to give the title compound as a syrup (5.5 g).
^{1}H NMR δ 0.78 - 0.87 (3H, m), 1.46 (3H, s), 1.74 - 1.87 (1H, m), 1.92 - 2.05 (1H, m), 2.54 (3H, s), 4.57 (1H, s), 7.28 - 7.34 (2H, m), 8.09 - 8.16 (2H, m).

Step 3: (RS)-2-Hydroxy-1-(4-methanesulfonylphenyl)-2-methyl-1-butanone

To a solution of the tertiary alcohol from Step 2 (4.5 g, 20.1 mmol) in CH_2Cl_2 (100 mL), MeOH (100 mL) and H_2O (25 mL) was added Oxone® (9 g). After 3 h at r.t. a second 9 g portion of Oxone® was added and the mixture was stirred overnight at r.t. The solvent was then removed under vacuum, and the residue was partitioned between EtOAc and H_2O. The organic phase was washed with H_2O and brine, and was then dried ($MgSO_4$), filtered, and evaporated. Purification was effected by flash chromatography (1:2 EtOAc: hexane) to give 5.5 g of the title compound as a tan coloured oil.
^{1}H NMR (300 MHz, acetone d_6) δ 0.84 - 0.92 (3H, m), 1.48 (3H, s), 1.74 - 1.87 (1H, m), 1.92 - 2.05 (1H, m), 3.18 (3H, s), 4.73 (1H, s), 7.99 - 8.05 (2H, m), 8.28 - 8.34 (2H, m).

Step 4: (RS)-1-(4-Methanesulfonylbenzoyl)-1-methylpropyl-2-isopropoxyacetate

To a solution of the tertiary alcohol methyl sulfone from step 3 (2.9 g, 11.3 mmol) and isopropoxy acetic acid (4.0 g, 34 mmol) in CH_2Cl_2 (100 mL) is added 1-cyclohexyl-3-(2-morpholinoethyl) carbodiimide metho-p-toluenesulfonate (CMC) (10 g, 24 mmol), followed by DMAP (0.66 g, 5.5 mmol). After stirring for 1 h., a further 2.5 g of CMC is added and the reaction is left stirring for an additional 1 h. Water is then added and the product is extracted with CH_2Cl_2. The CH_2Cl_2 layer is dried ($MgSO_4$), filtered, and evaporated. Purification is effected by flash chromatography, eluting with 1:6 EtOAc:toluene to give the title compound.

Step 5: (RS) 5-Ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one

The keto ester from Step 4 is dissolved in CH_3CN (80 mL) and isopropyl trifluoroacetate (1.2 mL, 8.7 mmol) is added, followed by DBU (1.6 mL, 11 mmol). The resulting solution is stirred for 20 h under gentle reflux. The solvent is then removed under vacuum, and the residue is partitioned between EtOAc and H_2O. The organic layer is washed with H_2O and brine, and is then dried ($MgSO_4$), filtered, and evaporated. Purification is effected by flash chromatography, eluting with 1:10 EtOAc: toluene to give the title compound.

EXAMPLE 210

3-(Cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

Step 1: 2-(Cylopropylmethoxy)acetic acid 2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one ester

A 50 L flask was charged with 12L dry THF and 95% sodium hydride (441 g, 17.5 mol)). The internal temperature was reduced to 12 °C, and an addition funnel was charged with cyclopropanemethanol (1198 g, 16.6 mol) in 2 L THF. This solution was added to the sodium hydride over 75 min, maintaining an internal temperature below 15 °C. The mixture was then warmed to room temperature and stirred 18h. Sodium chloroacetate (1413 g, 12.1 mol) was added, and the mixture was heated to reflux for 8.5h, then allowed to cool overnight. The thick slurry was cautiously quenched with water (100 mL), then 10 L of 2M HCl and 8 L of EtOAc were added. The layers were separated and the organic phase was washed with 1.5 L EtOAc. The combined organic phases were concentrated, then partitioned between 12 L EtOAc and 4 L brine. The organic phase was dried over $MgSO_4$ filtered and evaporated to give 1778g of a light yellow oil. To this material was added 2-bromo-2-methyl-1-(4-(methylsulfonyl)phenyl)propan-1-one (Ex. 109b Step A3, 2742g, 8.98 mol) and 15 L of anhydrous EtOH. Ethyldiisopropylamine (1706g, 13.2 mol) was added and the slurry was heated to reflux, giving a light yellow solution. After 30h, the solution was allowed to cool with periodic seeding with authentic product. Crystalization began at 46 °C. When the internal temperature reached 35 °C, 2L of water was added slowly via an addition funnel. The mixture was cooled to 4 °C in an ice-bath. The suspension was filtered and the crystals were washed with 20% aqueous EtOH (4 L), water (3 x 4 L), 25% aqueous EtOH (4 L), and ether (3 x 4 L), then air dried to give the title compound (1843 g, 5.20 mol, 58%).

Step 2: 3-(Cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one

A 50 L flask was charged with the ester from Step 2 (1843g, 5.20 mol), acetonitrile (23 L), isopropyltrifluoroacetate (1300 g, 8.33 mol), and DBU (1067 g, 7.01 mol). The solution was heated to reflux for 18h. The condensor was replaced with a still head, and 10.5 L of solvent was removed over 3h. The remaining solution was allowed to cool to 30 °C, then transferred into 40L of 0.3 M HCl with vigourous stirring, and seed crystals. The resulting slurry was stirred at room temperature for 18h, then filtered. The filter cake was washed with 2 x 5 L water, 2 L of 50% aqueous ethanol, and 3 L of ether. The solid was air-dried for 1h, then dried under vacuum overnight to give 1859 g of a white solid (still contains residual water). This material was suspended in 8 L ether, stirred for 26h, filtered and dried under vacuum to give 1371 g of the title compound. A further 130 g of material was obtained by reprocessing the aqueous acetonitrile and ether filtrate for a total of 1501 g.
^{1}H NMR (CD_3COCD_3) δ 0.28 (2H, m), 0.53 (2H, m), 1.17 (1H, m), 1.66 (6H, s), 3.17 (3H, s), 4.16 (2H, d), 8.03 (4H, s).